

International Publication No. WO 03/002519 A1

Job No.: 166-107787

Ref.: WO03002519A

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INTERNATIONAL PATENT OFFICE
WORLD ORGANIZATION FOR INTELLECTUAL PROPERTY

International application published on
the basis of the Patent Cooperation Treaty

INTERNATIONAL PUBLICATION NO. WO 03/002519 A1

International Patent Classification ⁷ :	C 07 C 233/73 275/36 311/21 A 61 K 31/167 31/17 31/18 C 07 C 271/58
International Filing No.:	PCT/EP02/06638
International Filing Date:	June 17, 2002
International Publication Date:	January 9, 2003
Priority	
Date:	June 29, 2001
Country:	DE
No.:	101 31 462.0
Filing Language:	German
Publication Language:	German

PHENOL DERIVATIVES AND THEIR USE IN MEDICAMENTS

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Designated States (national):

AE, AG, AL, AM, AT, AU, AZ, BA,
 BB, BG, BR, BY, BZ, CA, CH, CN,
 CO, CR, CU, CZ, DE, DK, DM, DZ,
 EC, EE, ES, FI, GB, GD, GE, GH,
 GM, HR, HU, ID, IL, IN, IS, JP, KE,
 KG, KP, KR, KZ, LC, LK, LR, LS,
 LT, LU, LV, MA, MD, MG, MK,

MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

Designated States (regional):

ARIPO Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Published

- With International Search Report.
- Before expiration of the period permitted for amendments to the claims. Will be republished if amendments are submitted.

For an explanation of the two-letter codes and other abbreviations, refer to the explanatory notes ("Guidance Notes on Codes and Abbreviations") at the beginning of each regular issue of the PCT Gazette

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LU, MC, NL, PT, SE, TR), OAPI
 Patent (BF, BJ, CF, CG, CI, CM, GA,
 GN, GQ, GW, ML, MR, NE, SN, TD,
 TG)

(57) Abstract: The invention relates to novel phenol derivatives, a method for the production of said derivatives and their use in medicaments.

The invention pertains to new phenol derivatives, processes for their manufacture and their use in medicaments.

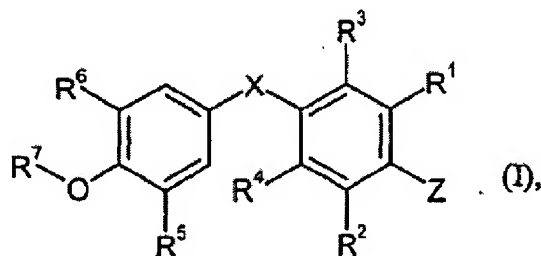
Oxamic acid derivatives, which possess cholesterol-lowering properties in mammals, are described in EP-A-580 550. The reduction in plasma cholesterol, especially LDL cholesterol, is emphasized as being a pharmacological property. Cholesterol-lowering effects are also described in EP-A-188 351 for certain diphenyl ethers with effects that resemble those of thyroid hormones.

In the same way, diphenyl ethers are disclosed as thyroid receptor ligands in WO 99/00353 and WO 00/39077. Further, diphenyl derivatives with properties that resemble thyroid hormones are described in the following patent applications: WO 98/57919, WO 99/26966, WO 00/51971 and WO 00/58279. Certain diphenyl sulfones for the treatment of hair loss are claimed in WO 00/72810 and WO 00/73265.

The objective of the present invention is to provide new compounds with pharmacological effects.

It has now been found that compounds of general formula (I), along with their pharmaceutically acceptable salts, solvates, hydrates and hydrates of the salts,

exhibit a pharmacological effect and are capable of being used as medicaments or for the manufacture of medicinal formulations:



in which

X stands for O, S, SO, SO₂, CH₂, CHF, CF₂ or for NR⁸ in which R⁸ stands for hydrogen or (C₁-C₄)-alkyl,

R¹ and R² are identical or different and stand for hydrogen or (C₁-C₄)-alkyl,

R³ and R⁴ are identical or different and stand for hydrogen, halogen, cyano, (C₁-C₆)-alkyl, CF₃, CHF₂, CH₂F, vinyl or (C₃-C₇)-cycloalkyl, whereby at least one of the two substituents is not identical to hydrogen,

R⁵ stands for hydrogen, (C₁-C₄)-alkyl or halogen,

R⁶ stands for (C₁-C₄)-alkyl, Br, Cl or for a group of formula -S-R⁹, -S(O)_n-R¹⁰, -NR¹¹-C(O)-R¹², -CH₂-R¹³ or -M-R¹⁴, in which

R⁹ stands for (C₁-C₁₀)-alkyl, (C₃-C₈)-cycloalkyl, (C₂-C₆)-alkenyl, (C₆-C₁₀)-aryl, (C₆-C₁₀)-arylmethyl or for a saturated, partially unsaturated or aromatic 5 to 10-membered heterocycle with up to four identical or different heteroatoms from the series N, O and/or S, whereby the aforementioned residues are optionally substituted by one, two or three identical or different substituents selected from the group comprising halogen, nitro, trifluoromethyl, hydroxy, oxo, cyano, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, carboxyl and (C₁-C₄)-alkoxycarbonyl,

n stands for the number 1 or 2,

R¹⁰ stands for OR¹⁵, NR¹⁶R¹⁷, (C₁-C₁₀)-alkyl, (C₃-C₈)-cycloalkyl, (C₂-C₆)-alkenyl, (C₆-C₁₀)-aryl, (C₆-C₁₀)-arylmethyl or for a saturated, partially unsaturated or aromatic 5 to 10-membered heterocycle with up to four identical or different heteroatoms from the series N, O and/or S, whereby the aforementioned residues are optionally substituted by one, two or three identical or different substituents selected from the group comprising halogen, hydroxy, oxo, cyano, nitro, amino, NR¹⁸R¹⁹, trifluoromethyl, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy that has optionally been substituted by R²⁰, (C₃-C₈)-cycloalkyl, (C₆-C₁₀)-aryl that in turn has optionally been substituted by halogen, (C₁-C₄)-alkyl, (C₁-C₄)-alkoxy, trifluoromethyl, nitro or cyano, -O-C(O)-R²¹, -O-C(O)-R²², -C(O)-NR²³R²⁴, -SO₂-NR²⁵R²⁶, -NH-C(O)-R²⁷ and -NH-C(O)-OR²⁸, whereby

R¹⁵, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷ and R²⁸ are identical or different and in each case stand for hydrogen, phenyl, benzyl, (C₁-C₆)-alkyl or (C₃-C₈)-cycloalkyl that are in turn optionally substituted singly or multiply, identically or differently, by halogen, hydroxy, amino, carboxyl, (C₁-C₄)-alkoxy, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkoxycarbonylamino, (C₁-C₅)-alkanoyloxy, a heterocycle or by phenyl that in turn is optionally substituted by halogen or hydroxy,

and

R¹⁶ and R¹⁷ are identical or different and, independently of one another, stand for hydrogen, straight-chain or branched (C₁-C₆)-alkyl that can be substituted singly or multiply, identically or differently, by mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, (C₁-C₄)-alkoxy,

(C₁-C₆)-alkoxycarbonyl, carboxyl, pyridyl or (C₆-C₁₀)-aryl, whereby the latter in turn is optionally substituted by halogen, trifluoromethyl, (C₁-C₆)-alkyl or (C₁-C₆)-alkoxy,

or for (C₆-C₁₀)-aryl that is optionally substituted by halogen, trifluoromethyl, (C₁-C₆)-alkyl or (C₁-C₆)-alkoxy, or for (C₃-C₈)-cycloalkyl, or for a 5- to 7-membered heterocycle that contains two nitrogen atoms, whereby the cycloalkyl group and the heterocycle are in turn optionally substituted by (C₁-C₄)-alkyl,

or

R¹⁶ and R¹⁷ together with the nitrogen atom to which they are bonded form a 5- to 7-membered saturated and optionally benzo-annellated heterocycle that can contain up to two further heteroatoms from the series N, O and/or S and that can be substituted by amino, (C₁-C₆)-alkyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkoxycarbonylamino or phenyl,

R¹¹ stands for hydrogen, straight-chain or branched (C₁-C₆)-alkyl that can be substituted singly or multiply, identically or differently, by mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, (C₁-C₄)-alkoxy, (C₁-C₆)-alkoxycarbonyl, carboxyl, pyridyl or (C₆-C₁₀)-aryl, whereby the latter in turn is optionally substituted by halogen, trifluoromethyl, (C₁-C₆)-alkyl or (C₁-C₆)-alkoxy, or for (C₃-C₈)-cycloalkyl, or for a 5- to 7-membered heterocycle that contains two nitrogen atoms, whereby the cycloalkyl group and the heterocycle are in turn optionally substituted by (C₁-C₄)-alkyl,

R¹² stands for straight-chain or branched (C₁-C₁₅)-alkyl that can be substituted by (C₃-C₈)-cycloalkyl, (C₁-C₄)-alkoxy, phenyl, phenoxy or benzyloxy, whereby the designated aromatic groups in turn can in each case be substituted identically or differently up to three times by halogen, (C₁-C₆)-alkyl or (C₁-C₄)-alkoxy,

or for (C₃-C₈)-cycloalkyl that can be substituted by (C₁-C₄)-alkoxy or phenyl,

or for (C₆-C₁₀)-aryl that can be substituted identically or differently up to three times by (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, halogen, cyano, amino, trifluoromethyl or phenyl,

or

for a 5-6 membered saturated or aromatic heterocycle, which has optionally been benzo-annellated, with up to two heteroatoms from the series N, O and/or S,

or

it signifies a group of formula -OR²⁹ or -NR³⁰R³¹

in which

R²⁹ stands for straight-chain or branched (C₁-C₆)-alkyl

and

R³⁰ and R³¹ are identical or different and, independently of one another, stand

for hydrogen, straight-chain or branched (C₁-C₁₂)-alkyl that can be substituted by aminocarbonyl, a group of formula -NR³²R³³, a 5-6 membered heteroaryl group that contains up to

3 heteroatoms selected from the group comprising N, O and/or S or that can be substituted by phenyl, whereby this phenyl group is optionally substituted identically or differently up to two times by halogen, (C₁-C₄)-alkyl, trifluoromethyl or (C₁-C₄)-alkoxy,

or for (C₃-C₈)-cycloalkyl that can be substituted by (C₁-C₄)-alkyl,

or for (C₆-C₁₀)-aryl that can be substituted identically or differently up to three times by halogen, (C₁-C₄)-alkyl, trifluoromethyl, (C₁-C₄)-alkoxy, amino, phenyl or phenoxy,

or

for a 5- to 7-membered saturated or unsaturated heterocycle that contains one or two nitrogen atoms and that is optionally substituted by (C₁-C₄)-alkyl or an oxo group,

whereby

R³² and R³³ are identical or different and, independently of one another, stand for hydrogen, (C₁-C₆)-alkyl, phenyl or (C₆-C₁₀)-arylsulfonyl,

or,

jointly with the nitrogen atom to which they are bonded, they form a 3-7 membered saturated heterocycle that optionally contains up to two further heteroatoms from the series N, O and/or S,

or

R³⁰ and R³¹, jointly with the nitrogen atom to which they are bonded, form a 4-7 membered saturated heterocycle that can contain up to two further heteroatoms from the series N, O and/or S and that can be substituted by amino, (C₁-C₆)-alkyl, (C₁-C₄)-alkanoyl, aminocarbonyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkoxycarbonylamino, phenyl or pyridyl,

R¹³ stands for a saturated, partially unsaturated or aromatic 5- to 10-membered heterocycle with up to three identical or different heteroatoms from the series N, O and/or S and is optionally substituted by one, two or three identical or different substituents selected from the group (C₁-C₄)-alkyl, hydroxy, oxo, (C₁-C₄)-alkoxy, halogen, cyano, carboxyl and (C₁-C₄)-alkoxycarbonyl,

or

R¹³ stands for the group -NR³⁴R³⁵ in which

R³⁴ and R³⁵ are identical or different and stand for hydrogen, (C₁-C₈)-alkyl that can be substituted by (C₆-C₁₀)-aryl, or for (C₃-C₈)-cycloalkyl, (C₆-C₁₀)-aryl or for a 5-6 membered heteroaryl group with up to three identical or different heteroatoms from the series N, O and/or S, whereby the aryl and heteroaryl groups are in turn optionally substituted, in each case identically or differently, either one or two times by hydroxy, amino, cyano, halogen, trifluoromethyl, (C₁-C₄)-alkyl, (C₁-C₄)-alkoxy, carboxyl, (C₁-C₄)-alkoxycarbonyl or mono-(C₁-C₄)-alkylaminocarbonyl or di-(C₁-C₄)-alkylaminocarbonyl,

M stands for C=O, CH(OH), CHF or CF₂,

and

R^{14} has the meaning indicated above for R^{10} ,

R^7 stands for hydrogen, (C_1-C_4) -alkyl or (C_1-C_4) -alkanoyl

and

Z stands for a group $NH-SO_2-R^{36}$, $NH-CO_2-R^{37}$, $NH-CO-NR^{38}R^{39}$ or $NH-CO-R^{40}$ in which R^{36} , R^{37} , R^{38} , R^{39} and R^{40} in each case stand for an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, heterocyclyl or heteroaryl group.

Preferable mention may be made of the following as the heterocycles in the definition of R^9 , R^{10} and R^{13} , respectively.

A 5- to 10-membered saturated, partially unsaturated or aromatic heterocycle with up to 4 heteroatoms from the series S, N and/or O, i.e., a monocyclic or bicyclic heterocycle that can contain one or more double bonds and that is linked via a ring carbon atom or optionally via a ring nitrogen atom. The following may be mentioned as examples: tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, piperidinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, piperazinyl, morpholinyl, azepinyl, 1,4-diazepinyl, furanyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrimidinonyl, pyridazinonyl, indolyl, benzo(b)thienyl, benzo(b)furyl, benzimidazolyl, indazolyl, quinolyl, isoquinolyl, naphthyridinyl, quinazolinyl.

From this list, the following are preferred: pyridyl, pyrimidinyl, pyridazinyl, pyrimidinonyl, pyridazinonyl and thienyl.

Within the framework of the invention, alkyl indicates a straight-chain or branched alkyl residue with, preferably, 1-15, 1-12, 1-10, 1-8, 1-6, 1-4 or 1-3 carbon atoms. A straight-chain or branched alkyl residue with 1-4 carbon atoms is preferred. By way of example, preferable mention may be made of: methyl, ethyl, n-propyl, isopropyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl and n-hexyl.

Within the framework of the invention, alkenyl indicates a straight-chain or branched alkenyl residue with, preferably, 2-6 or 2-4 carbon atoms. A straight-chain or branched alkenyl residue with 2-4 carbon atoms is preferred. By way of example, preferable mention may be made of: vinyl, allyl, isopropenyl and n-but-2-en-1-yl.

Within the framework of the invention, aryl indicates an aromatic residue with, preferably, 6-10 carbon atoms. Phenyl and naphthyl are the preferred aryl residues.

Within the framework of the invention, cycloalkyl indicates a cycloalkyl group with, preferably, 3-8, 3-7 or 3-6 carbon atoms. By way of example, preferable mention may be made of: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Within the framework of the invention, alkoxy preferably indicates a straight-chain or branched alkoxy residue with 1-6, 1-4 or 1-3 carbon atoms. A straight-chain or branched alkoxy

residue with 1-3 carbon atoms is preferred. By way of example, preferable mention may be made of: methoxy, ethoxy, n-propoxy, isopropoxy, t-butoxy, n-pentoxy and n-hexoxy.

Within the framework of the invention, alkoxycarbonyl preferably indicates a straight-chain or branched alkoxy residue with 1-6 or 1-4 carbon atoms, whereby the residue is linked via a carbonyl group. A straight-chain or branched alkoxycarbonyl residue with 1-4 carbon atoms is preferred. By way of example, preferable mention may be made of: methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl and t-butoxycarbonyl.

Within the framework of the invention, alkanoyl preferably indicates a straight-chain or branched alkyl residue with 1-6 or 1-4 carbon atoms, whereby the residue carries a double-bonded oxygen atom in the 1-position and is linked via the 1-position. A straight-chain or branched alkanoyloxy [sic] residue with 1-4 carbon atoms is preferred. By way of example, preferable mention may be made of: formyl, acetyl, propionyl, n-butyryl, i-butyryl, pivaloyl and n-hexanoyl.

Within the framework of the invention, alkanoyloxy preferably indicates a straight-chain or branched alkyl residue with 1-6, 1-5 or 1-3 carbon atoms, whereby the residue carries a double-bonded oxygen atom in the 1-position and is linked via an additional oxygen atom in the 1-position. A straight-chain or branched alkanoyloxy residue with 1-3 carbon atoms is preferred. By way of example, preferable mention may be made of: acetoxo, propionoxo, n-butyroxy, i-butyroxy, pivaloyloxy and n-hexanoyloxy.

Within the framework of the invention, monoalkylamino indicates an amino group with a straight-chain or branched alkyl substituent that preferably has 1-6, 1-4 or 1-2 carbon atoms. A straight-chain or branched monoalkylamino residue with 1-4 carbon atoms is preferred. By way of example, preferable mention may be made of: methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, n-pentylamino and n-hexylamino.

Within the framework of the invention, dialkylamino indicates an amino group with two identical or different, straight-chain or branched, alkyl substituents that preferably have, in each case, 1-6, 1-4 or 1-2 carbon atoms. Straight-chain or branched dialkylamino residues with 1-4 carbon atoms in each case are preferred. By way of example, preferable mention may be made of: *N,N*-dimethylamino, *N,N*-diethylamino, *N*-ethyl-*N*-methylamino, *N*-methyl-*N*-n-propylamino, *N*-isopropyl-*N*-n-propylamino, *N*-t-butyl-*N*-methylamino, *N*-ethyl-*N*-n-pentylamino and *N*-n-hexyl-*N*-methylamino.

Within the framework of the invention, monoalkylaminocarbonyl or dialkylaminocarbonyl indicates an amino group that is linked via a carbonyl group and that has one straight-chain or branched alkyl substituent or two identical or different, straight-chain or branched, alkyl substituents with, preferably, 1-4 or 1-2 carbon atoms in each case. By way of example, preferable mention may be made of: methylaminocarbonyl, ethylaminocarbonyl, isopropylaminocarbonyl,

t-butylaminocarbonyl, *N,N*-dimethylaminocarbonyl, *N,N*-diethylaminocarbonyl, *N*-ethyl-*N*-methylaminocarbonyl and *N*-t-butyl-*N*-methylaminocarbonyl.

Within the framework of the invention, monoacylamino indicates an amino group with a straight-chain or branched alkanoyl substituent that preferably has 1-6, 1-4 or 1-2 carbon atoms and that is linked via the carbonyl group. A monoacylamino residue with 1-2 carbon atoms is preferred. By way of example, preferable mention may be made of: formamido, acetamido, propionamido, n-butyramido and pivaloylamido.

Within the framework of the invention, alkoxycarbonylamino indicates an amino group with a straight-chain or branched alkoxycarbonyl substituent that preferably has 1-6 or 1-4 carbon atoms in the alkoxy residue and that is linked via the carbonyl group. An alkoxycarbonylamino residue with 1-4 carbon atoms is preferred. By way of example, preferable mention may be made of: methoxycarbonylamino, ethoxycarbonylamino, n-propoxycarbonylamino and t-butoxycarbonylamino.

Within the framework of the invention, 5-6 membered heteroaryl with up to 3 identical or different heteroatoms from the series S, N and/or O preferably indicates an aromatic heterocycle that is linked via a ring carbon atom of the heteroaromatic molecule and is optionally additionally linked via a ring nitrogen atom of the heteroaromatic molecule. By way of example, mention may be made of: furanyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, triazolyl, pyridyl, pyrimidinyl and pyridazinyl. Pyridyl, pyrimidinyl, pyridazinyl, furyl and thiazolyl are preferred.

Within the framework of the invention, a 3 to 7-, 4- to 7- or 5- to 7-membered saturated or partially unsaturated heterocycle with up to 3 identical or different heteroatoms from the series S, N and/or O preferably indicates a heterocycle that can contain one or two double bonds and that is linked via a ring carbon atom or a ring nitrogen atom. A 5- to 7-membered saturated heterocycle with up to 2 identical or different heteroatoms from the series S, N and/or O is preferred. By way of example, mention may be made of: tetrahydrofur-2-yl, tetrahydrofur-3-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolin-1-yl, piperidin-1-yl, piperidin-4-yl, 1,2-dihydropyridin-1-yl, 1,4-dihydropyridin-1-yl, piperazin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, azepin-1-yl, 1,4-diazepin-1-yl. Piperidinyl, piperazinyl, morpholinyl and pyrrolidinyl are preferred.

Within the framework of the invention, halogen includes fluorine, chlorine, bromine and iodine. Fluorine, chlorine or bromine are preferred.

Depending on the pattern of substituents, the compounds in accordance with the invention can exist in stereoisomeric forms that relate to one another either as in the case of an image and its mirror image (enantiomers) or that do not relate to one another as in the case of an image and its mirror image (diastereomers). The invention pertains to enantiomers or diastereomers and also to

their respective mixtures. Just as in the case of diastereomers, the racemic forms can be separated into the stereoisomerically uniform components in a known way.

Moreover, certain compounds can be present in tautomeric forms. This is known to the expert who is skilled in the art and such compounds are likewise included within the scope of the invention.

The compounds in accordance with the invention can also be present in the form of salts. Physiologically acceptable salts are preferred within the framework of the invention.

Physiologically acceptable salts can be salts of the compounds in accordance with the invention that are formed from inorganic or organic acids. The following are preferred: salts that are formed from inorganic acids such as e.g., hydrochloric acid, hydrobromic acid, phosphoric acid or sulfuric acid, or salts that are formed from organic carboxylic acids or sulfonic acids such as e.g., acetic acid, propionic acid, maleic acid, fumaric acid, malic acid, citric acid, tartaric acid, lactic acid, benzoic acid or methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid or naphthalenedisulfonic acid.

Physiologically acceptable salts can likewise be salts of the compounds in accordance with the invention that are formed from bases, such as e.g., metal salts or ammonium salts. The following are preferred examples: alkali metal salts (e.g., sodium or potassium salts), alkaline earth salts (e.g., magnesium or calcium salts) and also ammonium salts derived from ammonia or organic amines such as e.g., ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, dibenzylamine, N-methylmorpholine, dihydroabietylamine, 1-phenamine, methylpiperidine, arginine, lysine, ethylenediamine or 2-phenylethylamine.

The compounds in accordance with the invention can also be present in their solvate forms, and especially in their hydrate forms.

In addition, the invention also includes prodrugs of the compounds in accordance with the invention. In accordance with the invention, derivatives of the compounds of general formula (I) are designated "prodrugs" if these derivatives are themselves biologically less active, or they can even be inactive, though, after application, they are transformed into the corresponding biologically active form under physiological conditions (e.g., metabolically, solvolytically or in a different way).

Compounds of general formula (I) along with their pharmaceutically acceptable salts, solvates, hydrates and hydrates of the salts are preferred:

in which

X stands for O, S, CH₂ or CF₂,

R¹ and R² are identical or different and stand for hydrogen or methyl,

R^3 and R^4 are identical or different and stand for hydrogen, halogen, (C_1-C_4) -alkyl, CF_3 , CHF_2 , CH_2F , vinyl or (C_3-C_5) -cycloalkyl, whereby at least one of the two substituents is not identical to hydrogen,

R^5 stands for hydrogen, (C_1-C_3) -alkyl, fluorine, chlorine or bromine,

R^6 stands for (C_1-C_3) -alkyl or for a group of formula $-S(O)_2-R^{10}$, $-NR^{11}-C(O)-R^{12}$, $-CH_2-R^{13}$ or $-M-R^{14}$, in which

R^{10} stands for $NR^{16}R^{17}$, (C_1-C_8) -alkyl, (C_5-C_7) -cycloalkyl, phenyl, or benzyl, or for a saturated, partially unsaturated or aromatic 5- to 10-membered heterocycle with up to three identical or different heteroatoms from the series N, O and/or S, whereby the aforementioned residues are optionally substituted by one, two or three identical or different substituents selected from the group comprising halogen, hydroxy, oxo, cyano, nitro, amino, dimethylamino, trifluoromethyl, (C_1-C_4) -alkyl, (C_1-C_4) -alkoxy, (C_3-C_6) -cycloalkyl, and phenyl that in turn has optionally been substituted by halogen, (C_1-C_4) -alkyl, (C_1-C_4) -alkoxy, trifluoromethyl, nitro or cyano, $-C(O)-R^{22}$, $-C(O)-NR^{23}R^{24}$, $-SO_2-NR^{25}R^{26}$, $-NH-C(O)-R^{27}$ and $-NH-C(O)-OR^{28}$, whereby R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} and R^{28} are identical or different and in each case stand for hydrogen, phenyl, benzyl, (C_1-C_4) -alkyl or (C_5-C_7) -cycloalkyl that are in turn optionally substituted singly or multiply, identically or differently, by halogen, hydroxy, amino, carboxyl, (C_1-C_4) -alkoxy, (C_1-C_4) -alkoxycarbonyl, (C_1-C_4) -alkoxycarbonylamino or (C_1-C_5) -alkanoyloxy,

and

R^{16} and R^{17} are identical or different and, independently of one another, stand for hydrogen, straight-chain or branched (C_1-C_6) -alkyl that can be substituted singly or multiply, identically or differently, by (C_1-C_4) -alkoxy, (C_1-C_4) -alkoxycarbonyl, carboxyl, pyridyl or phenyl, whereby the latter, in turn, is optionally substituted by halogen, trifluoromethyl, (C_1-C_4) -alkyl or (C_1-C_4) -alkoxy,

or for phenyl that is optionally substituted by halogen, trifluoromethyl, (C_1-C_4) -alkyl or (C_1-C_4) -alkoxy, or for (C_5-C_7) -cycloalkyl, or for a 5- to 7-membered heterocycle that contains up to two nitrogen atoms, whereby the cycloalkyl group and the heterocycle are in turn optionally substituted by (C_1-C_4) -alkyl,

or

R^{16} and R^{17} together with the nitrogen atom to which they are bonded form a 5- to 7-membered saturated heterocycle that can contain up to two further heteroatoms from the series N, O and/or S and that can be substituted by amino, (C_1-C_4) -alkyl, (C_1-C_4) -alkoxycarbonyl, (C_1-C_4) -alkoxycarbonylamino or phenyl,

R^{11} stands for hydrogen, straight-chain or branched (C_1-C_4) -alkyl, benzyl, (C_3-C_7) -cycloalkyl, or for a 5- to 7-membered heterocycle that contains one or two nitrogen atoms, whereby the cycloalkyl group and the heterocycle are optionally substituted by (C_1-C_4) -alkyl,

R^{12} stands for straight-chain or branched (C₁-C₈)-alkyl that can be substituted by (C₃-C₇)-cycloalkyl, (C₁-C₄)-alkoxy, phenyl, phenoxy or benzyloxy, whereby the designated aromatic compounds can in turn, in each case, be substituted identically or differently up to three times by halogen, (C₁-C₄)-alkyl or (C₁-C₄)-alkoxy,

or

for phenyl that can be substituted identically or differently up to three times by (C₁-C₄)-alkyl, (C₁-C₄)-alkoxy, halogen, cyano, amino or trifluoromethyl,

or

it signifies a group of formula -OR²⁹ or -NR³⁰R³¹

in which

R^{29} stands for straight-chain or branched (C₁-C₄)-alkyl,

and

R^{30} and R^{31} are identical or different and, independently of one another, stand for hydrogen, a straight-chain or branched (C₁-C₈)-alkyl that can be substituted by phenyl that in turn is optionally substituted identically or differently up to two times by halogen, (C₁-C₄)-alkyl, trifluoromethyl or (C₁-C₄)-alkoxy,

or for (C₃-C₇)-cycloalkyl that can be substituted by (C₁-C₄)-alkyl,

or

for phenyl that can be substituted identically or differently up to three times by halogen, (C₁-C₄)-alkyl, trifluoromethyl, (C₁-C₄)-alkoxy or amino,

or

R^{30} and R^{31} jointly with the nitrogen atom to which they are bonded form a 5- to 7-membered saturated heterocycle that can contain up to two further heteroatoms from the series N, O and/or S and that can be substituted by amino, (C₁-C₄)-alkyl, (C₁-C₄)-alkanoyl, aminocarbonyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkoxycarbonylamino or phenyl,

R^{13} stands for a saturated, partially unsaturated or aromatic 5-6 membered heterocycle with up to three identical or different heteroatoms from the series N, O and/or S and that is optionally substituted by one, two or three identical or different substituents selected from the group (C₁-C₄)-alkyl, hydroxy, oxo, (C₁-C₄)-alkoxy, halogen, cyano, carboxyl and (C₁-C₄)-alkoxycarbonyl,

or

for the group -NR³⁴R³⁵ in which

R^{34} and R^{35} are identical or different and stand for hydrogen, (C₁-C₆)-alkyl that can be substituted by phenyl, or for (C₅-C₇)-cycloalkyl, phenyl or for a 5-6 membered heteroaryl group with up to three identical or different heteroatoms from the series N, O and/or S, whereby the phenyl and heteroaryl groups are in turn optionally substituted, in each case identically or

differently, either one or two times by hydroxy, amino, cyano, halogen, (C₁-C₄)-alkyl, trifluoromethyl, (C₁-C₄)-alkoxy, carboxyl or (C₁-C₄)-alkoxycarbonyl,

M stands for C=O, CH(OH), CHF or CF₂,

and

R¹⁴ has the meaning indicated above for R¹⁰,

R⁷ stands for hydrogen, methyl or acetyl.

Compounds of general formula (I) along with their pharmaceutically acceptable salts, solvates, hydrates and hydrates of the salts are especially preferred:

in which

X stands for O, S or CH₂,

R¹ and R² stand for hydrogen,

R³ and R⁴ are identical or different and stand for methyl, ethyl, propyl, isopropyl, cyclopropyl, trifluoromethyl, chlorine or bromine,

R⁵ stands for hydrogen,

R⁶ stands for (C₁-C₃)-alkyl or for a group of formula -S(O)₂-R¹⁰, -NH-C(O)-R¹², -CH₂-R¹³, -C(O)-R¹⁴ or -CH(OH)-R⁴¹, in which

R¹⁰ stands for phenyl or for a 5-6 membered heteroaryl group with up to three identical or different heteroatoms from the series N, O and/or S that are optionally substituted singly or doubly, identically or differently, by fluorine, chlorine, bromine, hydroxy, cyano, trifluoromethyl, (C₁-C₄)-alkyl, (C₁-C₄)-alkoxy, carboxyl or (C₁-C₄)-alkoxycarbonyl,

or

for the group -NR¹⁶R¹⁷, in which

R¹⁶ and R¹⁷ together with the nitrogen atom to which they are bonded form a 5-6 membered saturated heterocycle that can contain an additional heteroatom from the series N, O and/or S and can be substituted by (C₁-C₄)-alkyl,

R¹² stands for straight-chain or branched (C₁-C₆)-alkyl that is optionally substituted by phenoxy or benzyloxy,

R¹³ stands for a 5-6 membered heteroaryl group with up to three identical or different heteroatoms from the series N, O and/or S and that is optionally substituted by one or two identical or different substituents selected from the group (C₁-C₄)-alkyl, hydroxy, (C₁-C₄)-alkoxy, fluorine, chlorine, bromine, cyano, carboxyl and (C₁-C₄)-alkoxycarbonyl, or it stands for the group -NR³⁴R³⁵ in which

R³⁴ stands for (C₁-C₆)-alkyl or for (C₅-C₇)-cycloalkyl,

and

R³⁵ stands for benzyl that is optionally substituted in the phenyl ring by hydroxy, (C₁-C₄)-alkoxy, (C₁-C₄)-alkyl, trifluoromethyl, fluorine, chlorine or cyano,

R^{14} stands for a group of formula $-NR^{42}R^{43}$ in which

R^{42} stands for hydrogen, (C_1-C_6) -alkyl or (C_5-C_7) -cycloalkyl,

R^{43} stands for hydrogen or for (C_1-C_4) -alkyl that can be substituted by phenyl,

or

R^{42} and R^{43} together with the nitrogen atom to which they are bonded form a 5-6 membered saturated heterocycle that can contain one additional heteroatom from the series N, O and/or S and that can be substituted by (C_1-C_4) -alkyl,

and

R^{41} stands for phenyl that is optionally substituted singly or doubly, identically or differently, by fluorine, chlorine, bromine, (C_1-C_4) -alkyl, (C_1-C_4) -alkoxy, cyano, trifluoromethyl or (C_1-C_4) -alkoxycarbonyl,

R^7 stands for hydrogen.

Compounds of general formula (I) along with their pharmaceutically acceptable salts, solvates, hydrates and hydrates of the salts are quite especially preferred:

in which

X stands for CH_2 or, in particular, oxygen,

R^1 and R^2 stand for hydrogen,

R^3 and R^4 are identical or different and stand for methyl, ethyl, propyl, isopropyl, cyclopropyl, trifluoromethyl, chlorine or bromine,

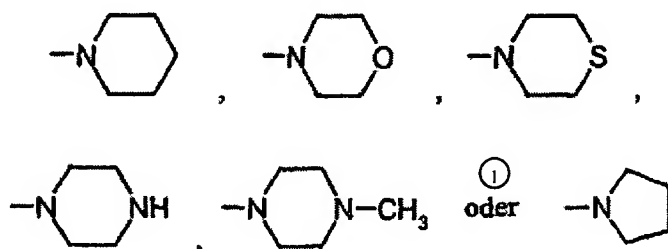
R^5 stands for hydrogen,

R^6 stands for methyl, ethyl, n-propyl, isopropyl or for a group of formula $-S(O)_2-R^{10}$, $-CH_2-R^{13}$ or $-C(O)-R^{14}$, in which

R^{10} stands for phenyl, pyridyl, pyrimidinyl or pyridazinyl that is optionally substituted singly or doubly, identically or differently, by fluorine, chlorine, bromine, hydroxy, cyano, trifluoromethyl, (C_1-C_4) -alkyl, (C_1-C_4) -alkoxy, carboxyl or (C_1-C_4) -alkoxycarbonyl,

or

for a group of formula



Key: 1 or

R^{13} stands for pyridyl, pyrimidinyl or pyridazinyl that is optionally substituted by one or two identical or different substituents selected from the group (C₁-C₄)-alkyl, hydroxy, (C₁-C₄)-alkoxy, fluorine, chlorine, bromine, cyano, carboxyl and (C₁-C₄)-alkoxycarbonyl, or it stands for the group -NR³⁴R³⁵ in which

R^{34} stands for (C₁-C₄)-alkyl or for (C₅-C₇)-cycloalkyl,

and

R^{35} stands for benzyl that is optionally substituted in the phenyl ring by hydroxy, (C₁-C₄)-alkoxy, (C₁-C₄)-alkyl, trifluoromethyl, fluorine, chlorine or cyano,

and

R^{14} stands for a group of formula -NR⁴²R⁴³ in which

R^{42} stands for hydrogen, (C₁-C₄)-alkyl or (C₅-C₇)-cycloalkyl,

and

R^{43} stands for hydrogen or for (C₁-C₄)-alkyl that can be substituted by phenyl, and

R^7 stands for hydrogen.

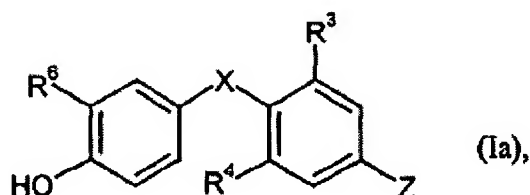
The definitions of residues listed above and indicated in general terms or in preferred ranges apply both to the end products of formula (I) and also correspondingly to the starting substances or intermediate products that are required in each case for their manufacture.

The detailed residue definitions in the combinations in question or in the preferred combinations are also replaced as desired by the residue definitions in other combinations, independent of the combinations in question of the indicated residues.

Compounds of general formula (I), in which X stands for oxygen, are of particular importance.

Compounds of general formula (I), in which R^6 stands for isopropyl, are of particular importance.

Of quite significant importance are compounds of general formula (Ia)



in which

X stands for CH₂ or, in particular, O,

R³ and R⁴ are identical or different and stand for bromine, trifluoromethyl, ethyl, cyclopropyl and, in particular, methyl or chlorine,

and

R⁶ stands for isopropyl.

Within the framework of the present invention, the following definitions apply within the meanings of Z.

R³⁶ preferably stands for unsubstituted or substituted alkyl with 1-10 carbon atoms or for alkenyl with 2-4 carbon atoms or for phenyl, naphthyl, benzyl, thiophenyl, imidazolyl, thiazolyl that are in each case unsubstituted or substituted.

R³⁶ stands for alkyl with 1-10 carbon atoms that has optionally been substituted by phthalimido or oxo, or for vinyl or allyl, or for phenyl, unsubstituted or substituted by C₁-C₄-alkoxy, C₁-C₄-alkyl, halogen, ureylene, hydroxy, nitro, alkylcarbonyl, alkylcarbonylamino and/or bis-benzylamino, or for benzyl, unsubstituted or substituted by nitro, or for thiophenyl that has optionally been substituted by alkoxycarbonyl, oxazolyl or the group -CH₂-NH-CO-chlorophenyl, or for imidazolyl that has optionally been substituted by alkyl, or for thiazolyl or naphthyl that in each case has optionally been substituted by alkylcarbonylamino.

R³⁷ preferably stands for an unsubstituted or substituted alkyl group with 1-10 carbon atoms, or for an unsubstituted or substituted cycloalkyl group with 5-8 carbon atoms, or for unsubstituted or substituted phenyl or benzyl.

R³⁷ stands, in particular, for alkyl with 1-10 carbon atoms or preferably 1-6 carbon atoms that has optionally been substituted by phenoxy, or for phenyl or benzyl that is, in each case, unsubstituted or substituted by alkoxy or phenyl, or for cyclohexyl that has optionally been substituted by alkyl.

R³⁸ preferably stands for hydrogen, unsubstituted or substituted alkyl with 1-6 carbon atoms, or it stands for phenyl that has optionally been substituted by alkyl.

R³⁹ preferably stands for unsubstituted or substituted alkyl with 1-8 carbon atoms or it stands for phenyl, benzyl, naphthyl, anthraquinonyl, tetrahydronaphthyl, tetrahydroquinoline, benzotriazolyl, benzodioxolanyl, thiadiazolyl, pyrazanyl, morpholinyl, thiazolyl or pyrrolidinyl that are in each case either unsubstituted or substituted, or it stands for phenoxycarbonyl or phenylcarbonyl that is in each case either unsubstituted or substituted, or it stands for unsubstituted or substituted cycloalkyl with 4-8 carbon atoms.

R³⁹ stands, in particular, for alkyl with 1-6 carbon atoms, unsubstituted or substituted by cyano or alkoxycarbonyl, or it stands cyclohexyl, unsubstituted or substituted by alkyl, or it stands

for phenyl that is unsubstituted or substituted in each case by halogenalkyl, alkyl, halogen, unsubstituted or substituted phenoxy, phenyl, $-\text{SO}_2$ -phenyl, benzyl, carboxy, alkoxy, nitro, cyano and/or alkoxycarbonyl, or it stands for benzyl that has optionally been substituted by halogenalkyl, or it stands for phenoxycarbonyl that has been substituted by alkoxy, or it stands for phenylcarbonyl, or it stands for anthraquinonyl, or it stands for tetrahydronaphthyl that has been substituted by alkoxy, or it stands for phenyl-substituted benztriazole, or it stands for naphthyl, or it stands for benzdioxolanyl, or it stands for thiadiazolyl that has been substituted by alkyl, or it stands for morpholinyl, or it stands for thiazolyl that has been substituted by halogen and/or cyano.

R^{38} and R^{39} together with the nitrogen atom to which they are bonded also form an unsubstituted or substituted saturated or unsaturated 5- to 7-membered heterocycle with up to 3 heteroatoms from the series S, N and/or O.

R^{38} and R^{39} together with the nitrogen atom to which they are bonded preferably form a morpholine residue, a pyrrolidine residue, a tetrahydroquinoline residue or a pyrazan residue that has been substituted by one or more alkoxycarbonyl, alkyl and/or oxo substituents.

R^{40} preferably stands for unsubstituted or substituted alkyl with 1-8 carbon atoms, or it stands for unsubstituted or substituted alkylene with 2-4 carbon atoms, or it stands for a unsubstituted or substituted residue selected from the following: cycloalkyl with 3-8 carbon atoms, aryl or heteroaryl such as, in particular, benzyl, phenyl, furanyl, thiophenyl, isooxazolyl, pyridyl, imidazolyl, pyrazinyl, quinolinyl, pyrazolyl, triazolyl, pyrrolyl, heterocyclyl with 5-8 ring atoms and at least one O, N or S atom such as, in particular, tetrahydrofuranyl, tetrahydroisoquinoline, dihydrothiophene, thiazolidinyl, imidazolinyl, dihydropyridinyl, piperidinyl, or it stands for phenylalkoxy.

R^{40} stands for, in particular, alkyl with 1-6 carbon atoms that is unsubstituted or that is substituted by benzyl, alkylcarbonylamino, unsubstituted or morpholinalkyloxy-substituted phenyl, benzyloxy, cyclopentyl, alkylcarbonyloxy, alkoxycarbonyl, unsubstituted or halogen- and alkyl-substituted phenoxy, alkylcarbonylamino, piperidinyl, alkoxy, dialkylamino, pyridinyl, alkyloxyalkoxy, tetrahydrofuranyl, benzdioxane, imidazolyl, triazolyl, phenylcarbonylamino, benzdioxolane and/or benzthiazolidinethioxolyl,

or it stands for phenyl, unsubstituted or substituted by nitro, alkyl, halogen or phenoxy,

or it stands for cyclohexyl, unsubstituted or trichlorophenylalkoxyalkyl-substituted furanyl, dialkyl substituted isooxolyl, unsubstituted or oxo-substituted tetrahydrofuranyl, alkoxycarbonyl-substituted tetrahydroisoquinoline, dihydrothiophene, oxotetrahydrothiazole, oxo- and alkyl-substituted dihydroimidazolyl, unsubstituted or phenyl-substituted cyclopropyl or cyclopentyl, unsubstituted or cyclopropyl- and hydroxyl-substituted pyridinyl, phenyl- or alkyl-substituted pyrazolyl, pyrazinyl, quinolinyl, tetrahydronaphthalenyl, alkyl-substituted pyrrolyl,

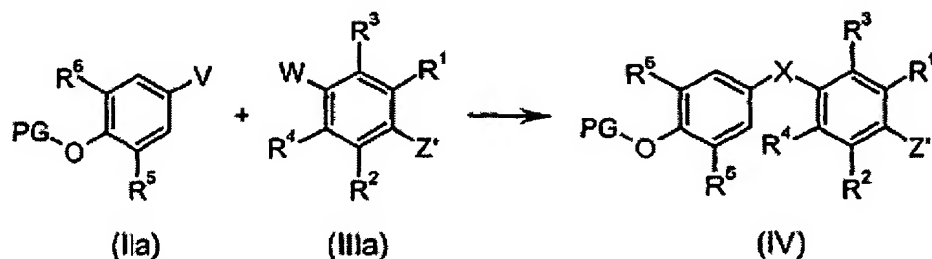
or it stands for phenyl-substituted vinyl.

The compounds in accordance with the invention of general formula (I) can be manufactured by reacting reactive phenol derivatives of general formulas (IIa-c) with reactive phenyl derivatives of general formulas (IIIa-c) in accordance with one of the following process variants [A], [B] or [C] optionally in the presence of inert solvents and catalysts and optionally with isolation of the intermediate products of general formulas (IV), (IVa), (IVb) or (IVc), or directly, to give compounds of formula (I), whereby the substituents R^1 , R^2 , R^3 , R^4 , R^5 and R^6 and also X and Z in each case have the meanings that are indicated above,

Z' has the meaning indicated for Z, or it stands for a nitro group, an amino group, an acetamido group, a benzyloxycarbonylamino group, or for a tert-butoxycarbonylamino group, and

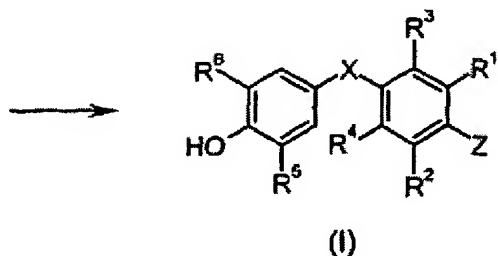
PG stands for a suitable group that provides protection (protecting group).

Process variant [A]:

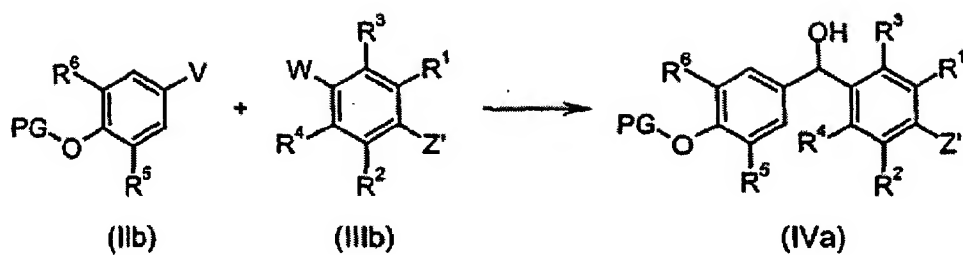


$V = F, Cl, Br, I, B(OH)_2$; $W = OH, SH, NH_2$

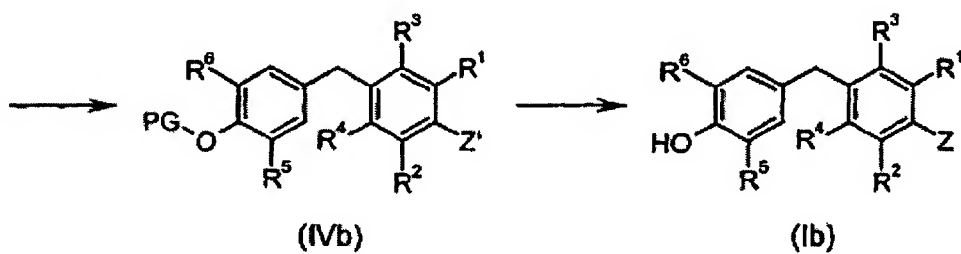
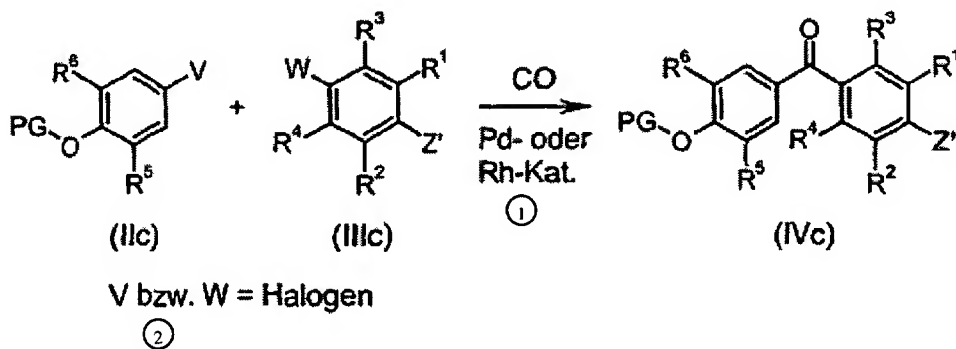
① bzw. $V = OH, SH, NH_2$; $W = F, Cl, Br, I, B(OH)_2$



Key: 1 or

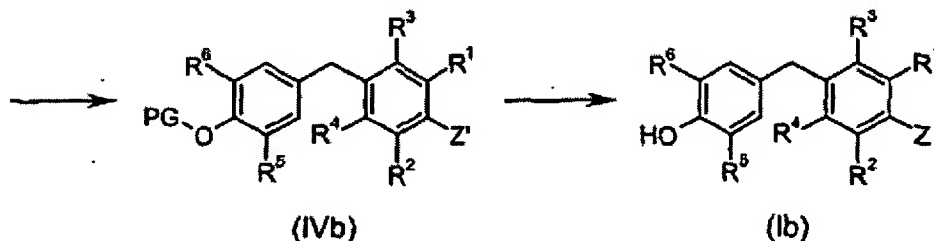
Process variant [B]:

$V = CHO$; $W = Li, MgCl, MgBr, Cu$ organic group, Ce organic group or Zn organic group, or $V = Li, MgCl, MgBr, Cu$ organic group, Ce organic group or Zn organic group; $W = CHO$

Process variant [C]:

Key: 1 Pd catalyst or Rh catalyst

2 or



Concerning the catalysts, mention may be made by way of example of coupling catalysts such as Pd compounds, Rh compounds and/or Cu compounds.

By way of example, mention may be made of the following as the reactive groups V or W: halogen, hydroxy, CH_2Br , mercapto, amino, CHO, Li, or magnesium derivatives, tin derivatives, boron derivatives, copper derivatives, cerium derivatives or zinc derivatives.

The phenol derivatives of general formulas (IIa-c) that can be used in accordance with the invention are known or can be manufactured in accordance with known methods (see e.g., Ogata et al., *Tetrahedron* **26**, 731-736 (1970); Borsche et al., *Justus Liebigs Ann. Chem.* **450**, 82 (1926); Pickholz, *J. Chem. Soc.*, 685 (1946); Truce, *J. Amer. Chem. Soc.* **73**, 3013, 3015 (1951); Fraenkel et al., *J. Amer. Chem. Soc.*, **102**, (9), 2869-2880 (1980); Cacciola et al., *Bioorg. Med. Chem. Lett.* **6** (3), 301-306 (1996); Allen, *Synth. Commun.* **29** (3), 447-456 (1999); WO 00/58279).

The phenyl derivatives of general formulas (IIIa-c) are also known or can be manufactured in accordance with known methods (see e.g., van de Bunt, *Recl. Trav. Chim. Pays-Bas* **48**, 131 (1929); Valkanas, *J. Chem. Soc.*, 5554 (1963); Thea et al., *J. Org. Chem.* **50**, 1867-1872 (1985); Baker et al., *J. Chem. Soc.*, 2303-2306 (1948); Miller et al., *J. Med. Chem.* **23** (10), 1083-1087 (1980)).

The reaction of the starting compounds (IIa-c) with (IIIa-c) generally is done at normal pressure. However, it can also be carried out using increased or reduced pressure.

The reaction can be carried out in the temperature range of -100°C to $+200^\circ\text{C}$, and preferably between -78°C and $+150^\circ\text{C}$, in the presence of inert solvents. Preferable mention may be made of the following as inert solvents: dimethyl sulfoxide (DMSO), dimethylformamide (DMF), N-methyl-2-pyrrolidinone (NMP), tetrahydrofuran (THF), diethyl ether, dichloromethane, etc.

Depending on the specific pattern of substituents, intermediate products of formulas (IV), (IVa), (IVb) or (IVc) can also be produced during the reaction of (IIa-c) and (IIIa-c) in which, for

example, the substituent Z' stands for a nitro group, an amino group, an acetamido group, a benzyloxycarbonylamino group or a tert-butoxycarbonylamino group, or X stands for a CH(OH) group or a C(O) group, whereby the intermediate products are then reacted further in accordance with conventional methods, either with or without the isolation of these intermediate stages, to give compounds of formula (I).

Depending on the meanings of the substituents R¹, R², R³, R⁴, R⁵ and R⁶, it can be expedient or necessary to vary these in the individual process steps, though within the indicated scope of their meanings.

The term protecting groups (protecting groups: PG, PG¹, PG²) is to be understood in the present patent application to mean those groups in the starting products and/or the intermediate products that protect functional groups that are present, such as e.g., carboxyl groups, amino groups, mercapto groups or hydroxy groups, and that are conventional in preparative organic chemistry. The groups that have been protected in this way can then be transformed into the free functional groups in a simple way under known conditions.

The compounds of formula (I) in accordance with the invention exhibit a surprising and valuable pharmacological spectrum of effects and they can thus be used as multifaceted medicaments. In particular, they can be used for all indications that can be treated via natural thyroid gland hormones such as, by way of example and preferably, depression, goiter or cancer of the thyroid gland. Arteriosclerosis, hypercholesterolemia and dyslipidemia can be treated preferentially with the compounds of formula (I) in accordance with the invention. In addition to this, adiposity and corpulence (obesity) and cardiac insufficiency can also be treated, and postprandial reduction of the triglycerides can be achieved.

The compounds are also suitable for the treatment of certain diseases of the respiratory tract, namely pulmonary emphysema in particular, and for the medication-based encouragement of pulmonary maturation.

The compounds are also suitable for the treatment of pain conditions and migraines and for neuronal repair (remyelination) as well as for the treatment of Alzheimer's disease.

The compounds are also suitable for the treatment of osteoporosis, cardiac rhythm disorders, cases of hypothyroidism and diseases of the heart.

In addition, the compounds can also be used for the promotion and regeneration of hair growth and for the treatment of diabetes.

The active substances in accordance with the invention open up an additional treatment alternative and represent an enrichment of pharmacy. The compounds in accordance with the invention exhibit an improved spectrum of effects in comparison to the known and previously used thyroid gland preparations. They preferentially excel by virtue of their high specificity, good compatibility and less marked side effects, especially in cardiac circulation cases.

The efficacy of the compounds in accordance with the invention can be tested, e.g., in vitro, by means of the T3 Promoter Assay Cell Test that is described in the following section.

The test is carried out with a stable transfected human HepG2 hepatocarcinoma cell that expresses a luciferase gene under the control of a thyroid hormone regulated promoter. The vector used for transfection carries a minimal thymidine kinase promoter with a thyroid hormone responsive element (TRE) upstream of the luciferase gene, whereby this thyroid hormone responsive element comprises two inverted palindromes of 12 Bp and an 8 Bp spacer in each case.

In order to carry out the test, the cell cultures are spaced out in Eagle's Minimal Essential Medium on 96-well plates with the following additions: glutamine, tricine [N-(tris(hydroxymethyl)methyl)glycine], sodium pyruvate, nonessential amino acids (L-Ala, L-Asn, L-Asp, L-Pro, L-Ser, L-Glu, Gly), insulin, selenium and transferrin. The cultures are initially cultured for 48 h at 37°C in a 10% CO₂ atmosphere. Serial dilutions of the test substances or the reference compound (T3, T4) and costimulator retinoic acid are then added to the test cultures and these are incubated for an additional 48 or 72 h as before. Each substance concentration is tested in the form of four replicates. In order to determine the luciferase that is induced by T3 or other substances, the cells are subsequently lysed by adding a buffer that contains Triton and luciferin (from the Promega company) and then they are immediately measured luminometrically. The EC₅₀ values for each compound are calculated.

The compounds in accordance with the invention also exhibit surprisingly advantageous properties in the tests that are described in the following section.

Test descriptions for discovering pharmacologically active substances

The substances to be investigated in vivo regarding their effect on lowering serum cholesterol are administered orally to male mice with body weights between 25 and 35 g. The animals are subdivided into groups with equal numbers of animals, generally n = 7-10, one day prior to the start of the experiment. Drinking-water and animal feed are available to the animals ad libitum throughout the entire experiment. The substances are administered orally once per day over a period of 7 days. For this purpose, the test substances are dissolved in e.g., a solution comprising Solutol HS 15 + ethanol + sodium chloride solution (0.9%) in the ratio 1 + 1 + 8 or in a solution comprising Solutol HS 15 + sodium chloride solution (0.9%) in the ratio 2 + 8. The application of the dissolved substances is done at a volume of 10 mL/kg of body weight by means of an. The control group comprised animals treated in exactly the same way though they received only the solvent (10 mL/kg of body weight) without the test substance.

Prior to the first application of the substance, blood is taken from each mouse in order to determine the serum cholesterol level (preliminary value) by puncturing the retro-orbital venous plexus. Using a probang, the test substance is then administered to the animals for the first time. 24

h following the final application (on the 8th day after the start of treatment), blood is again taken from each animal in order to determine the serum cholesterol level by puncturing the retro-orbital venous plexus. The blood samples are centrifuged and, after recovering the serum, the cholesterol is determined photometrically by means of an EPOS Analyzer 5050 (Eppendorf-Gerätebau, Netheler & Hinz GmbH, Hamburg). The determination is done using a conventional enzyme test (Boehringer Mannheim, Mannheim).

The effect of the test substances on the serum cholesterol concentration is determined by subtracting the cholesterol value for the 1st sample of blood that was taken (preliminary value) from the cholesterol value for the 2nd sample of blood taken (following treatment). The differences of all cholesterol values within a group are averaged and a comparison is made relative to the average value of the differences in the control group.

Statistical evaluation is done by means of the Student's t test after prior checking of the variances for homogeneity.

Substances that lower the serum cholesterol of the treated animals in a statistically significant manner ($p < 0.05$) by at least 10% compared to the control group are regarded as being pharmacologically effective.

At the end of the experiment, the animals are weighed and sacrificed after the final blood sample is taken. The hearts are removed and weighed in order to check for potential cardiovascular side effects from influence of the substance. An effect on the cardiac circulation system can be established via a significant increase in heart weight. A change in body weight can be utilized as an additional parameter for the action of the substance.

In an analogous manner, use can be made of e.g., NMRI mice, ob/ob mice, Wistar rats or Zucker fa/fa rats as the experimental animals for this test.

A further in vivo test in which the compounds in accordance with the invention exhibit surprisingly advantageous properties is the animal model of the cholesterol-fed rat (A. Taylor et al., *Molecular Pharmacology* 52, 542-547 (1997); Z. Stephan et al., *Atherosclerosis* 126, 53-63 (1996)).

In addition, the cholesterol-lowering effect of the compounds in accordance with the invention can also be checked using normocholesterolemic dogs via the oral administration of the test substance over a period of 5-7 days.

Among other methods, the determination of the expression of the mRNA of the "HCN2" ion channel ("hyperpolarization activated cyclic nucleotide gated channel") in the hearts of mice or rats can be utilized for the further investigation of potential cardiovascular side effects as a result of the influence of the substance (see also: Trost et al., *Endocrinology* 141 (9), 3057-3064 (2000); Gloss et al., *Endocrinology* 142 (2), 544-550 (2001); Pachuki et al., *Circulation research* 85, 498-503 (1999)).

HCN2 Assay

The quantification of the mRNA of the "hyperpolarization activated cyclic nucleotide gated" cation channel (HCN2) in rat hearts was done by means of real-time PCR (TaqMan PCR; Heid et al., *Genome Res.* 6 (10), 986-994). In order to do this, the entire RNA is isolated, by means of RNAeasy columns (from the Qiagen company) following the preparation of the hearts, and then it is digested with DNase and transcribed into cDNA (SUPERScript-II RT cDNA synthesis kit, from the Gibco company). The HCN2-mRNA is determined using an ABI Prism 7700 apparatus (from the Applied Biosystems company). The sequence of the "forward" and "reverse" primer is as follows: 5'-GGGAATCGACTCCGAGGTC-3' or 5'-GATCTTGGTGAAACGCACGA-3'; that of the fluorescing sample is: 5'-6FAMACAAGACGGCCCGTGCCTTACGC-TAMRA-3 (FAM = the fluorescence dye 6-carboxyfluorescein; TAMRA = the quencher 6-carboxytetramethylrhodamine). As a result of the 5'-exonuclease activity of the Taq polymerase, the fluorescence dye FAM is split off during the polymerase chain reaction and, as a result, the previously quenched fluorescence signal is obtained. The number of the cycle in which the fluorescence intensity was 10 standard deviations above the background fluorescence is termed the so-called "threshold cycle" (Ct value). The relative expression of the HCN2-mRNA that was calculated by means of this is then standardized in terms of the expression of the ribosomal protein L32.

This assay can also be carried out in an analogous way using the hearts of mice. In this case, the sequence of the "forward" and "reverse" primer is as follows:

5'-CGAGGTGCTGGAGGAATACC-3' or 5'-CTAGCCGGTCAATAGCCACAG-3'; that of the fluorescing sample is: 5'-6FAM-CATGATGCGGCGTGCTTTGAG-TAMRA-3.

All conventional application forms can be considered for the application of the compounds of general formula (I), i.e., oral, parenteral, via inhalation, nasal, sublingual, buccal, rectal, or external such as e.g., transdermal and especially preferably oral or parenteral. In the case of parenteral application, mention may be made especially of intravenous application, intramuscular application and subcutaneous application, e.g., in the form of a subcutaneous deposit. Oral application is quite especially preferred.

In this connection, the active substances can be administered on their own or in the form of preparations. Among others, tablets, capsules, pellets, coated tablets, pills, granules, solid and liquid aerosols, syrups, emulsions, suspensions and solutions are suitable as oral preparations. In this regard, the active substance has to be present in such a quantity that a therapeutic effect is achieved. In general, the active substance can be present in a concentration of 0.1-100 wt%, and especially 0.5-90 wt%, and preferably 5-80 wt%. In particular, the concentration of the active

substance should amount to 0.5-90 wt%, i.e. the active substance should be present in quantities that are adequate for achieving the indicated dosage latitude.

For this purpose, the active substances can be transformed into conventional preparations in a way that is known as such. This is done using inert, nontoxic, pharmaceutically suitable carrier substances, ancillary substances, solvents, vehicles, emulsifiers and/or dispersing agents.

By way of example, the following may be listed as ancillary substances: water, nontoxic organic solvents such as e.g., paraffins, plant oils (e.g., sesame oil), alcohols (e.g., ethanol, glycerin), glycols (e.g., poly(ethylene glycol)), solid carrier substances such as natural or synthetic mineral dust (e.g., talcum or silicates), sugars (e.g., lactose), emulsifying agents, dispersing agents (e.g., polyvinylpyrrolidone) and lubricating agents (e.g., magnesium sulfate).

In the case of oral application, the tablets can of course also contain additions such as sodium citrate together with additives such as starch, gelatin and similar materials. Aqueous preparations for oral application can also be mixed with taste-improvers or dyes.

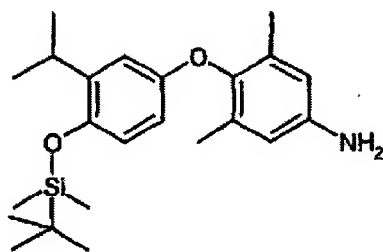
In the case of oral application, dosages of 0.001-5 mg/kg of body weight, and preferably 0.001-3 mg/kg of body weight, are preferably applied every 24 h.

The new active substances can be administered on their own or, if required, even in combination with other active substances, preferably from the group of CETP inhibitors, antidiabetic agents, antioxidants, cytostatic agents, calcium antagonists, agents that lower blood pressure, thyroid hormones, HMG-CoA reductase inhibitors, inhibitors of HMG-CoA reductase gene expression, squalene synthesis inhibitors, ACAT inhibitors, agents that promote the perfusion of blood, thrombocyte aggregation inhibitors, anticoagulants, angiotensin-II receptor antagonists, cholesterol absorption inhibitors, MTP inhibitors, aldose reductase inhibitors, fibrates, niacin, anorectic agents, lipase inhibitors and PPAR agonists.

The following embodiment examples are intended to elucidate the invention by way of example, though without restricting the scope of patent protection. The following examples are generated analogously to the processes indicated above

Examples

1. 4-(4-{[tert-butyl(dimethyl)silyl]oxy}-3-isopropylphenoxy)-3,5-dimethylaniline

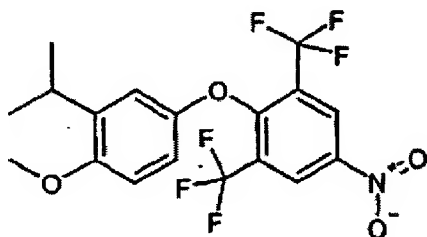


420 mg of 4-(4-amino-2,6-dimethylphenoxy)-2-isopropylphenol (manufactured analogously to EP 0580550) in 5 mL of THF are mixed in portions, under argon, with 62 mg of NaH (60%). Stirring is carried out for a sufficient duration at room temperature until no further evolution of gas is observed. 257 mg of tert-butyldimethylsilyl chloride is added and the reaction mixture is stirred overnight. The reaction mixture is mixed with methylene chloride/pH 7 buffer, and the aqueous phase is extracted 1x with methylene chloride; the combined organic phases are washed 1x with pH 7 buffer and 1x with a saturated NaCl solution, and then the organic phase is dried and the solvent is removed in vacuo. 473 mg (77%) of 4-(4-{[tert-butyl(dimethyl)silyl]oxy}-3-isopropylphenoxy)-3,5-dimethylaniline is obtained via chromatographic purification (toluene:acetonitrile 8:1).

300 MHz $^1\text{H-NMR}$ (CDCl_3): 0.17, s, 6H; 0.97, s, 9H; 1.12, d, 6H; 2.03, s, 6H; 3.23, hept., 1H; 3.47, s, ^①breit, 2H; 6.27, dd, 1H; 6.38, s, 2H; 6.57, d, 1H; 6.77, dd, 1H.

Key: 1 broad

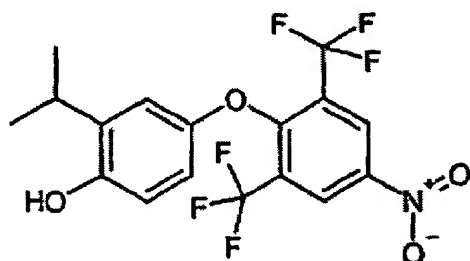
2. 1-methoxy-2-isopropyl-4-[4-nitro-2,6-bis(trifluoromethyl)phenoxy]benzene



113 mg (0.68 mmol) of 3-isopropyl-4-methoxyphenol is dissolved in 20 mL of DMSO together with 200 mg (0.68 mmol) of 2,6-bis-trifluoromethyl-4-nitrochlorobenzene and 104 mg of potassium carbonate (0.75 mmol) and the mixture is stirred for 3 h at 80°C. Dilution is done with water and ethyl acetate, and then the organic phase is extracted 3 times with a sodium chloride solution; drying is done over sodium sulfate and then the solvent is removed in vacuo. Chromatographic purification (toluene:cyclohexane = 1:1) yields 215 mg (75%) of 1-methoxy-2-isopropyl-4-[4-nitro-2,6-bis(trifluoromethyl)phenoxy]benzene.

200 MHz $^1\text{H-NMR}$ (CDCl_3): 1.15, d, 6H; 3.29, sep, 1H; 3.80, s, 3H; 6.46, dd, 1H; 6.71, m, 2H; 8.80, s, 2H.

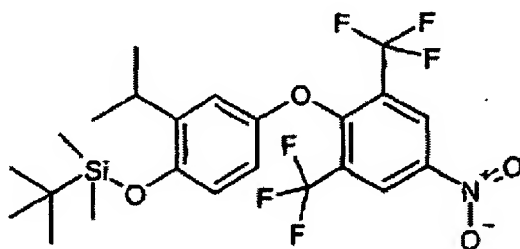
3. 2-isopropyl-4-[4-nitro-2,6-bis(trifluoromethyl)phenoxy]phenol



1 g (2.36 mmol) of 1-methoxy-2-isopropyl-4-[4-nitro-2,6-bis(trifluoromethyl)phenoxy]benzene is dissolved in 100 mL of dichloromethane and mixed under argon at 0°C with 2.36 mL (2.36 mmol) of boron tribromide (1 molar solution in dichloromethane). Stirring is carried out for 4 h at 22°C followed by admixture with an additional 2.36 mL of boron tribromide. After 2 h, the reaction solution is washed once with 50 mL of saturated sodium hydrogen carbonate solution and dried over sodium sulfate, filtered and evaporatively concentrated under reduced pressure. Purification of the raw product is done using 70 g of silica gel (elution tol/ethyl acetate; 9:1). 0.7 g (72%) of 2-isopropyl-4-[4-nitro-2,6-bis(trifluoromethyl)phenoxy]phenol is obtained.

200 MHz $^1\text{H-NMR}$ (DMSO-d_6): 1.10, d, 6H; 3.15, sep, 1H; 6.48, dd, 1H; 6.69, m, 2H; 8.74, s, 2H; 9.23, s, 1H.

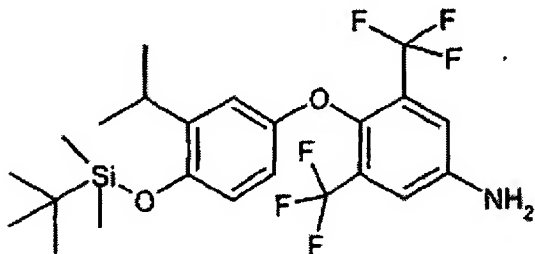
4. 1-(*tert*-butyldimethylsilanyloxy)-2-isopropyl-4-[4-nitro-2,6-bis(trifluoromethyl)phenoxy]benzene



59 mg (1.47 mmol) of sodium hydride (60% suspension in mineral oil) is suspended in 30 mL of tetrahydrofuran and mixed at 0 °C with 0.6 g (1.47 mmol) of 2-isopropyl-4-[4-nitro-2,6-bis(trifluoromethyl)phenoxy]phenol (dissolved in 5 mL of tetrahydrofuran). Stirring is carried out for 10 min at this temperature and then 0.24 g (1.61 mmol) of *tert*-butylchlorodimethylsilane (dissolved in 5 mL of tetrahydrofuran) is added. After 5 h at 22 °C, 50 mL of water is added thereto and the mixture is extracted with 50 mL of ethyl acetate. The organic phase is washed once with 50 mL of saturated sodium hydrogen carbonate solution, dried over sodium sulfate, filtered and evaporatively concentrated under reduced pressure. Purification of the raw product is done using 70 g of silica gel (elution: toluene). 0.6 g (78%) of 1-(*tert*-butyldimethylsilanyloxy)-2-isopropyl-4-[4-nitro-2,6-bis(trifluoromethyl)phenoxy]benzene is obtained.

200 MHz ^1H -NMR (DMSO- d_6): 0.20, s, 6H; 0.98, s, 9H; 1.09, d, 6H; 3.21, sep, 1H; 6.58, dd, 1H; 6.73, m, 2H; 8.76, s, 2H.

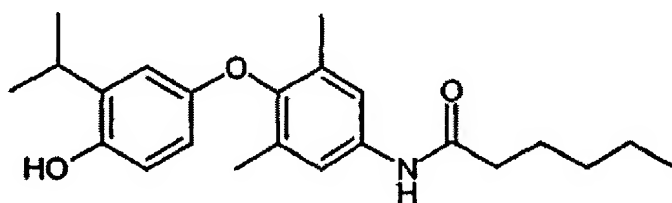
5. 4-[1-(*tert*-butyldimethylsilanyloxy)-2-isopropyl-4-phenoxy]-3,5-bis(trifluoromethyl)aniline



0.58 g (1.1 mmol) of 1-(*tert*-butyldimethylsilyloxy)-2-isopropyl-4-[4-nitro-2,6-bis(trifluoromethyl)phenoxy]benzene is dissolved in 150 mL of tetrahydrofuran and hydrogenated using 200 mg Pd/carbon (10%) for 18 h at 3 bar. Suctional filtration over kieselguhr is then done and the solvent is removed in vacuo. Purification of the raw product is done using 70 g of silica gel (elution: toluene). 0.43 g (78%) of 4-[1-(*tert*-butyldimethylsilyloxy)-2-isopropyl-4-phenoxy]-3,5-bis(trifluoromethyl)aniline is obtained.

200 MHz $^1\text{H-NMR}$ (DMSO- d_6): 0.17, s, 6H; 0.97, s, 9H; 1.07, d, 6H; 3.18, sep, 1H; 6.00, s, 2H; 6.37, dd, 1H; 6.57, d, 1H; 6.69, d, 1H; 7.20, s, 2H.

6. N-[4-(4-hydroxy-3-isopropylphenoxy)-3,5-dimethylphenyl]hexanamide



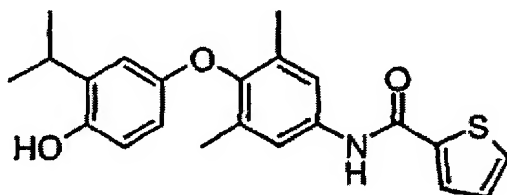
473 mg of 4-(4-[[*tert*-butyl(dimethyl)silyl]oxy]-3-isopropylphenoxy)-3,5-dimethylaniline is dissolved in 10 mL of THF and then mixed sequentially with 165 mg of hexanoyl chloride and 150 mg of dimethylaminopyridine. Stirring is carried out for 16 h at room temperature and then an additional 37 mg of hexanoyl chloride is added thereto; stirring is carried out for 1 h at room temperature and then an additional 37 mg of hexanoyl chloride are added thereto. After 1 h, the reaction mixture is mixed with 1.1 mL of a 1N tetrabutylammonium fluoride solution in THF and stirring is carried out for 1 h. The solvent is removed in vacuo and the residue is taken up in dichloromethane and pH 7 buffer solution. The aqueous phase is extracted with dichloromethane and the combined organic phases are washed with saturated NaCl solution, dried and subjected to rotary evaporation. Chromatographic purification and crystallization from ether/petroleum ether yields 335 mg (73%) of N-[4-(4-hydroxy-3-isopropylphenoxy)-3,5-dimethylphenyl]hexanamide.

200 MHz $^1\text{H-NMR}$ (CDCl_3): 0.92, t, 3H; 1.21, d, 6H; 1.38, m, 4H; 1.72, m, 4H; 1.72, m, 2H; 2.10, s, 6H; 2.35, t, 2H; 3.16, hept., 1H; 4.49, s, 1H; 6.29, dd, 1H; 6.58, d, 1H; 6.72, d, 1H; 7.03, s, breit, 1H; 7.22, m.

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Key: 1 broad

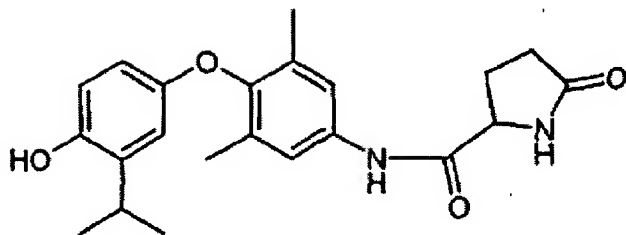
7. N-[4-(4-hydroxy-3-isopropylphenoxy)-3,5-dimethylphenyl]-2-thiophene carboxamide



150 mg of 4-(4-([*tert*-butyl(dimethyl)silyl]oxy)-3-isopropylphenoxy)-3,5-dimethylaniline is dissolved in 3 mL of THF and then mixed sequentially with 68 mg of thiophene-2-carbonyl chloride and 57 mg of dimethylaminopyridine. Stirring is carried out for 16 h at room temperature and then 0.4 mL of a 1N tetrabutylammonium fluoride solution in THF is added, followed by mixing and stirring for 2 h. The solvent is removed in vacuo and the residue is taken up in dichloromethane and pH 7 buffer solution. The aqueous phase is extracted with dichloromethane and the combined organic phases are washed with saturated NaCl solution, dried and subjected to rotary evaporation. Chromatographic purification and crystallization from ether/petroleum ether yield 104 mg (69%) of N-[4-(4-hydroxy-3-isopropylphenoxy)-3,5-dimethylphenyl]-2-thiophene carboxamide.

300 MHz $^1\text{H-NMR}$ (CDCl_3): 1.19, d, 2H; 3.22, hept., 1H; 6.28, dd, 1H; 6.67, m, 2H; 7.12, dd, 1H; 7.45, s, 2H; 7.55, dd, 1H; 7.87, dd, 1H; 8.00, s, 1H; 9.28, s, 1H.

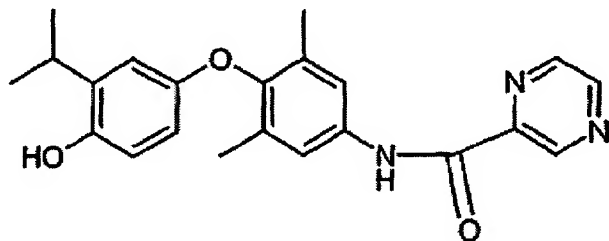
8. N-[4-(4-hydroxy-3-isopropylphenoxy)-3,5-dimethylphenyl]-5-oxoprolinamide



150 mg of 4-(4-{{tert-butyl(dimethyl)silyl}oxy}-3-isopropylphenoxy)-3,5-dimethylaniline is dissolved in 5 mL of dichloroethane and then mixed sequentially with 71 mg of DMAP, 75 mg of 5-oxoproline, 78 mg of HOBT and 112 mg of EDC. Stirring is carried out for 16 h and then 6 mL of a 1M tetrabutylammonium fluoride solution (in THF) is added and stirring is carried out for an additional 4 h. The solvent is removed in vacuo and the residue is taken up in dichloromethane and water; the aqueous phase is extracted with dichloromethane once and the combined organic phases are washed with saturated NaCl solution, dried and the solvent is removed in vacuo. Chromatography and reprecipitation from dichloromethane by means of petroleum ether yield 55 mg (36%) of N-[4-(4-hydroxy-3-isopropylphenoxy)-3,5-dimethylphenyl]-5-oxoprolinamide.

300 MHz ^1H -NMR (CDCl_3): 1.21, d, 6H; 2.11, s, 6H; 2.48, m, 4H; 3.16, hept., 1H; 4.30, m, 1H; 6.17, s, 1H; 6.39, dd, 1H; 6.57, d, 1H; 6.71, d, 1H; 7.30, s, 2H; 7.76, s, 1H.

9. N-[4-(4-hydroxy-3-isopropylphenoxy)-3,5-dimethylphenyl]-2-pyrazinyl carboxamide

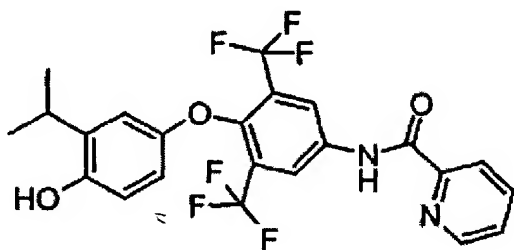


150 mg of 4-(4-{{tert-butyl(dimethyl)silyl}oxy}-3-isopropylphenoxy)-3,5-dimethylaniline is dissolved in 5 mL of dichloroethane and then mixed sequentially with 71 mg of DMAP, 72 mg of 2-pyrazinecarboxylic acid, 78 mg of HOBT and 112 mg of EDC. Stirring is carried out for 16 h

and then 6 mL of 1M tetrabutylammonium fluoride solution (in THF) is added and stirring is carried out for an additional 4 h. The solvent is removed in vacuo and the residue is taken up with dichloromethane and water; the aqueous phase is extracted once with dichloromethane and the combined organic phases are washed with saturated NaCl solution, dried and the solvent is removed in vacuo. Chromatography and reprecipitation from dichloromethane by means of petroleum ether yield 93 mg (59%) of N-[4-(4-hydroxy-3-isopropylphenoxy)-3,5-dimethylphenyl]-2-pyrazine carboxamide.

300 MHz ^1H -NMR (CDCl_3): 1.21, d, 6H; 2.17, s, 6H; 3.17, sept., 1H; 4.53, s, 1H; 6.32, dd, 1H; 6.61, d, 1H; 6.76, d, 1H; 7.51, s, 2H; 8.59, dd, 1H; 8.81, d, 1H; 9.52, d, 1H; 9.60, s, 1H.

10. N-[4-(4-hydroxy-3-isopropylphenoxy)-3,5-bis(trifluoromethyl)phenyl]-2-pyridine carboxamide



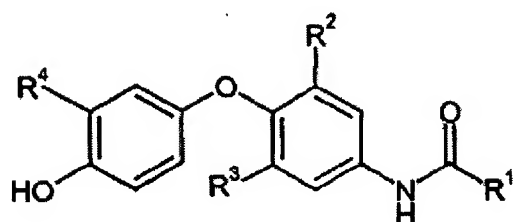
180 mg of

4-(4-{[tert-butyl(dimethyl)silyl]oxy}-3-isopropylphenoxy)-3,5-bis(trifluoromethyl)aniline are dissolved in 5 mL of dichloroethane and then mixed sequentially with 90 mg of DMAP, 90 mg of pyridine-2-carboxylic acid, 99 mg of HOBt and 140 mg of EDC. The reaction mixture is stirred overnight at room temperature and then mixed with 6 mL of a 1M tetrabutylammonium fluoride solution (in THF). Stirring is carried out for 4 h at room temperature, the solvent is removed in vacuo and the residue is taken up with dichloromethane and water. The aqueous phase is extracted with dichloromethane and the combined organic phases are washed with saturated NaCl solution, dried and the solvent is removed in vacuo. Chromatographic purification yields 149 mg (84%) of N-[4-(4-hydroxy-3-isopropylphenoxy)-3,5-bis(trifluoromethyl)phenyl]-2-pyridine carboxamide.

300 MHz ^1H -NMR (CDCl_3): 1.20, d, 6H; 3.13, hept., 1H; 4.47, s, breit, 1H; 6.37, dd, 1H; 6.61, d, 1H; 6.69, d, 1H; 7.56, dd, 1H; 7.97, dd, 1H; 8.31, d, 1H; 8.39, s, 2H; 8.64, d, 1H; 10.30, s, 1H.

Key: 1 broad

11. Additional carboxamides of the general formula were synthesized in accordance with the general working procedures of methods A and B



Method A for the synthesis of carboxamides

The listed carboxamides are manufactured in a 2-stage sequence by means of automated parallel synthesis from 4-[1-(*tert*-butyldimethylsilyloxy)-2-isopropyl-4-phenoxy]-3,5-bis(trifluoromethyl)aniline and the corresponding carbonyl chlorides with subsequent desilylation in accordance with the following general working procedure. The purity of the compounds manufactured is determined by means of HPLC. Characterization of the compounds is done by means of LC-MS.

General working procedure for the synthesis of carboxamides

1 molar equivalent of the carbonyl chloride is introduced into the reaction vessel and dissolved in 0.4 mL of THF. 1 molar equivalent of 4-[1-(*tert*-butyldimethylsilyloxy)-2-isopropyl-4-phenoxy]-3,5-bis(trifluoromethyl)aniline and 1 molar equivalent of DMAP are then added together, and in each case, a 0.13M solution in THF. The mixture is stirred for 17.5 h at room temperature.

The reaction mixture is now mixed with 1 molar equivalent of TBAF (0.37M solution in tetrahydrofuran). Stirring is then carried out for 1.5 h at 23°C and dilution is carried out with 1 mL of buffer solution (pH 4); stirring is carried out for 20 min followed by filtration over a cartridge filled with 1.3 g of Extrelut. Final washing is conducted with ethyl acetate and the solvent is

removed in vacuo. The residue is taken up in DMF and evaporative concentration is carried out once again.

Method B for the synthesis of carboxamides

The listed carboxamides are manufactured in a 2-stage sequence by means of automated parallel synthesis from

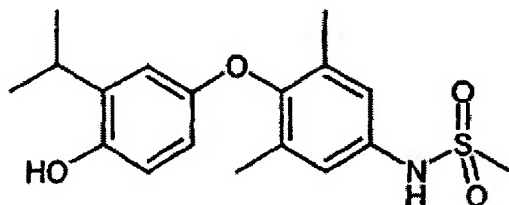
4-[1-(*tert*-butyldimethylsilanyloxy)-2-isopropyl-4-phenoxy]-3,5-bis(trifluoromethyl)aniline and the corresponding carbonyl chlorides with subsequent desilylation in accordance with the following general working procedure. The purity of the compounds that were manufactured is determined by means of HPLC. Characterization of the compounds is done by means of LC-MS.

General working procedure for the synthesis of carboxamides

2.5 molar equivalents of the carboxylic acid are introduced into the reaction vessel. 0.09 mmol of 4-[1-(*tert*-butyldimethylsilanyloxy)-2-isopropyl-4-phenoxy]-3,5-bis(trifluoromethyl)aniline is added thereto in the form of a 4.0 molar solution in dichloromethane. The following are then added sequentially at 23°C: 2.5 molar equivalents of DMAP in the form of a 0.1 molar solution in dichloromethane, 2.5 molar equivalents of HOBT in the form of a 3.0 molar solution in dichloromethane along with 3.0 molar equivalents of EDC in the form of a 0.14 molar solution in dichloromethane; the mixture is then stirred for 4 days at 23°C.

Next, the reaction mixture is combined with 10 molar equivalents of TBAF (1M solution in tetrahydrofuran). Stirring is then carried out for 16 h at 23°C and dilution is carried out with 3 mL of dichloromethane followed by washing with 3 mL of water. It is then filtered through a cartridge filled with 1.3 g of Extrelut, followed by evaporative concentration under reduced pressure. The remaining residue is purified by means of preparative HPLC (Kromasil; 100 C18; 50 x 20 mm column from the Grom company; acetonitrile/water gradient 30:70 - 90:10).

12. N-[4-(4-hydroxy-3-isopropylphenoxy)-3,5-dimethylphenyl]methane sulfonamide



750 mg of

4-[1-(*tert*-butyldimethylsilyloxy)-2-isopropyl-4-phenoxy]-3,5-dimethylaniline is dissolved in 500 mL of THF and then mixed with 446 mg of methanesulfonyl chloride and 475 mg of DMAP. Stirring is carried out for 17 h at room temperature and the solvent is removed in vacuo; the residue is taken up in dichloromethane and then this solution is shaken with buffer solution (pH 4); the organic phase is dried and the solvent is removed in vacuo.

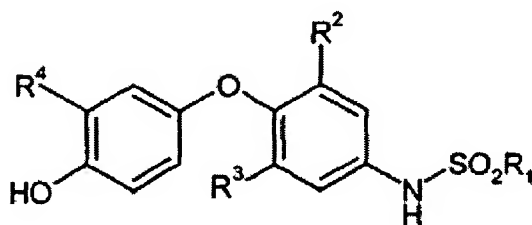
The residue is dissolved in 40 mL of THF and the solution is mixed with 1.88 mL of a 1M TBAF solution in THF. Stirring is carried out for 1 h at room temperature and the solution is then mixed with buffer solution (pH 7) and dichloromethane; the phases are separated and the organic phase is extracted with a saturated NaCl solution. After drying, the solvent is removed in vacuo. 400 mg (59%) are obtained.

400 MHz $^1\text{H-NMR}$ (CDCl_3): 1.21, d, 6H; 2.11, s, 6H; 3.03, s, 3H; 3.17, sept., 1H; 3.72, m, 1H; 4.40, s, breit, 1H; 6.28, dd, 1H; 6.59, d, 1H; 6.73, d, 1H; 6.96, s, 1H.

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Key: 1 broad

13. Additional sulfonamides of the general formula were synthesized in accordance with the general working procedures of method C



Method C for the synthesis of sulfonamides

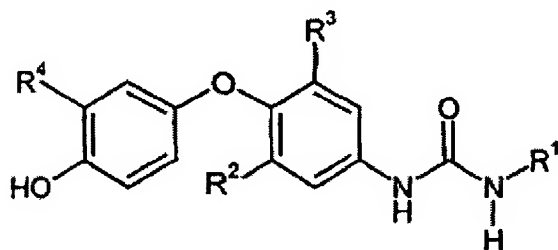
The listed sulfonamides are manufactured in a 2-stage sequence by means of automated parallel synthesis from 4-[1-(*tert*-butyldimethylsilyloxy)-2-isopropyl-4-phenoxy]-3,5-bismethylaniline and the corresponding sulfonyl chlorides with subsequent desilylation in accordance with the following general working procedure. The purity of the manufactured compounds is determined by means of HPLC. Characterization of the compounds is done by means of LC-MS.

General working procedure for the synthesis of the sulfonamides.

2 molar equivalents of the sulfonyl chloride are introduced into the reaction vessel and dissolved in THF. 1 molar equivalent of 4-[1-(*tert*-butyldimethylsilyloxy)-2-isopropyl-4-phenoxy]-3,5-bismethylaniline and 2 molar equivalents of DMAP are added thereto in the form of a 0.06M or 0.12M solution in THF. The mixture is then stirred for 20 h at room temperature.

The reaction mixture is mixed with a quantity of acidic ion exchanger that just covers the tip of a spatula, and a quantity of basic ion exchanger that just covers the tip of a spatula; the mixture is stirred for 15 min, filtered and the solvent is removed in vacuo. The residue is once again taken up in THF and mixed with 1 molar equivalent of TBAF (1.1M solution in tetrahydrofuran). Stirring is then carried out for 22 h at 23°C; the mixture is mixed with a quantity of acidic ion exchanger that just covers the tip of a spatula, stirred for 10 min and filtered; the solvent is then removed in vacuo. The residue is taken up in DMF and once again evaporatively concentrated.

14. Method D for the synthesis of primary ureas



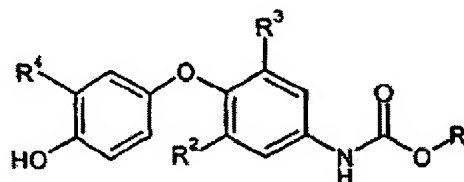
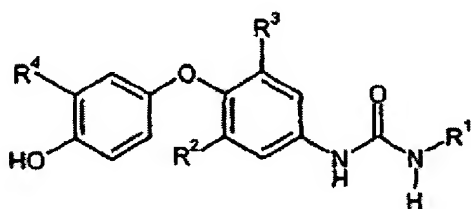
The described ureas are manufactured in a 2-stage sequence by means of automated parallel synthesis from 4-(4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-isopropylphenoxy)-3,5-dimethylaniline and the corresponding isocyanates with subsequent desilylation in accordance with the following general working procedure. The purity of the manufactured compounds is determined by means of HPLC. Characterization of the is done by means of LC-MS.

General working procedure for the synthesis of the ureas.

1.5 molar equivalents of the isocyanate are introduced into the reaction vessel. 0.14 mmol of 4-(4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-isopropylphenoxy)-3,5-dimethylaniline in the form of a 0.072 molar solution in dioxane along with 0.1 molar equivalents of phosphazene base are added

thereto at 23°C. The mixture is then stirred for 4 h at 80°C. 150 mg of aminomethylated polystyrene are then added thereto and stirring is carried out for an additional 15 h at 23°C. After adding 3.0 molar equivalents of TBAF (1M solution in tetrahydrofuran) 23°C [sic], the mixture is stirred for 1 h at 23°C. The mixture is diluted with 8 mL of dichloromethane and washed once with, in each case, 2 mL of a 1N hydrochloric acid and 2 mL of a 1N sodium hydroxide solution. The mixture is then filtered through a cartridge filled with 1.3 g of Extrelut (upper phase) and 1.3 g of silica gel 60 (lower phase) (elution with 5 mL of dichloromethane). The desired ureas are obtained after evaporative concentration under reduced pressure.

15. Method E for the synthesis of secondary ureas and carbamates



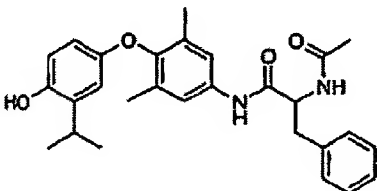
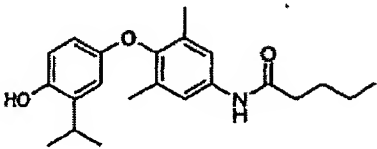
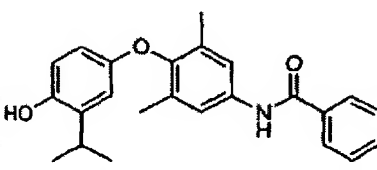
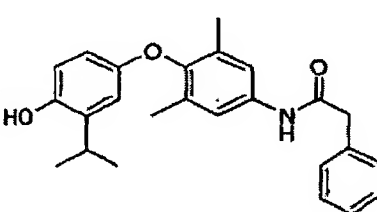
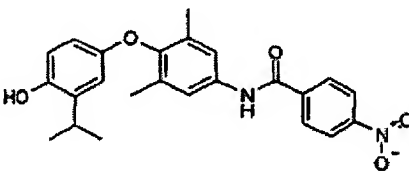
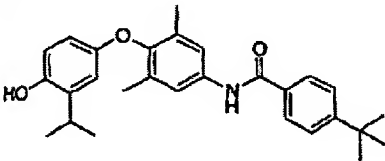
The additional listed carbamates and sec. ureas are manufactured in a 2-stage sequence by means of automated parallel synthesis from 4-(4-{[tert-butyl(dimethyl)silyl]oxy}-3-isopropylphenoxy)-3,5-dimethylaniline and the corresponding esters of chloroformic acid or the corresponding carbamoyl chlorides with subsequent desilylation in accordance with the following general working procedure. The purity of the manufactured compounds is determined by means of HPLC. Characterization of the compounds is done by means of LC-MS.

General working procedure for the synthesis of the carbamates and secondary ureas.

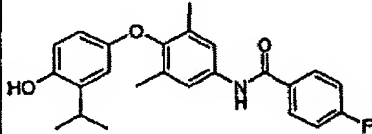
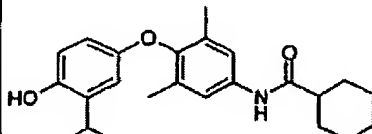
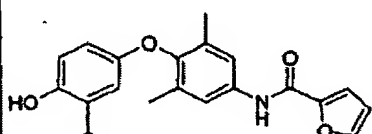
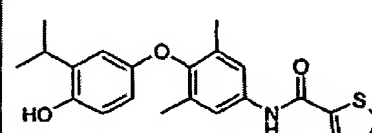
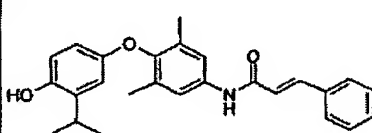
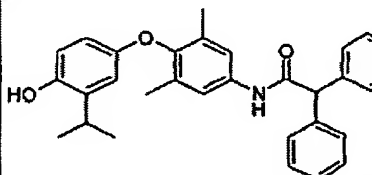
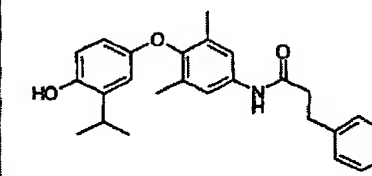
1.25 molar equivalents of the chlorocarbonyl compound are introduced into the reaction vessel. 0.10 mmol of 4-(4-{[tert-butyl(dimethyl)silyl]oxy}-3-isopropylphenoxy)-3,5-dimethylaniline in the form of a 0.045 molar solution in 1,2-dichloroethane along with 2.0 molar equivalents of N-ethyl-diisopropylamine in the form of a 0.154 molar solution in 1,2-dichloroethane are then added thereto at 23°C. The mixture is stirred for 2 days at 65°C. 100 mg of aminomethylated polystyrene are then added thereto and stirring is carried out for an additional 15 h at 65°C. After cooling to 5°C, 3.0 molar equivalents of TBAF (1M solution in tetrahydrofuran) are added thereto

and the mixture is heated to 23°C within a period of 30 min while being stirred. After adding 1ML of 1N hydrochloric acid, the reaction mixture is filtered through a cartridge filled with 1.3 g of Extrelut (upper phase) and 1.3 g of silica gel 60 (lower phase) (elution with 8 mL of ethyl acetate). Following evaporative concentration under reduced pressure, the remaining residue is purified by means of preparative HPLC (Kromasil; 100 C18; 50 x 20 mm column from the Grom company; acetonitrile/water gradient 30:70 - 90:10).

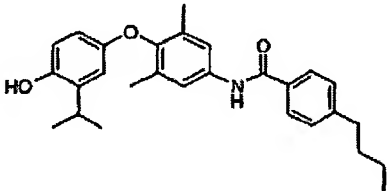
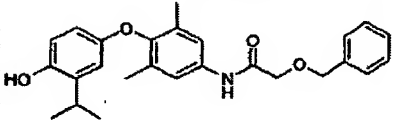
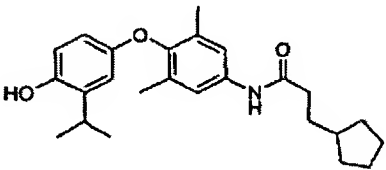
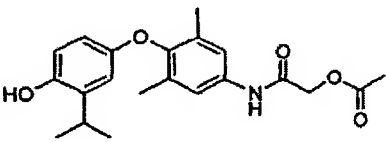
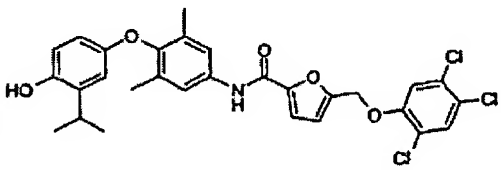
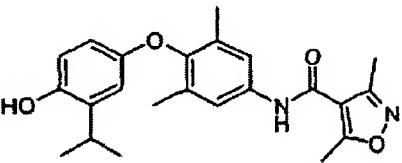
The following examples are manufactured in accordance with the general process procedures.

① Beispiel-Nr.	② Struktur	③ Retentionszeit	④ Methode
16			
17			
18			
19		4,7	A
20		4,8	A
21		5,3	A

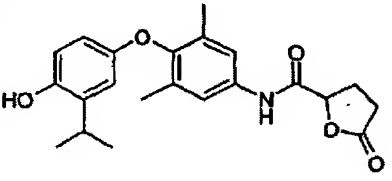
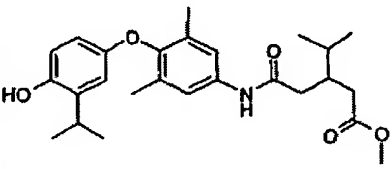
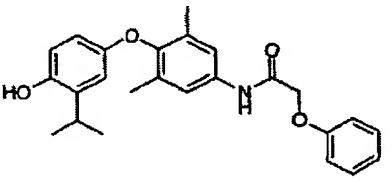
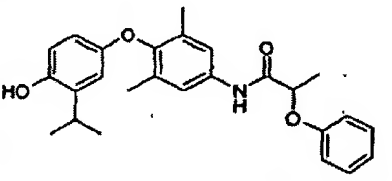
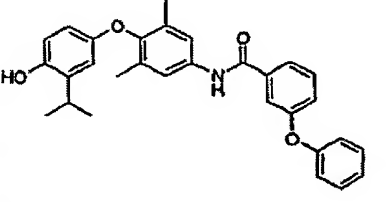
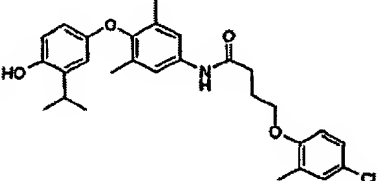
Key: 1 Example No.
 2 Structure
 3 Retention time
 4 Method

① Beispiel-Nr.	② Struktur	③ Retentionszeit	④ Methode
22		4,8	A
23		5	A
24		4,5	A
25		4,7	A
26		4,9	A
27		5,2	A
28		4,9	A

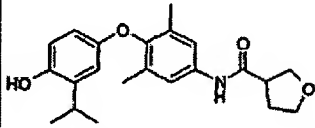
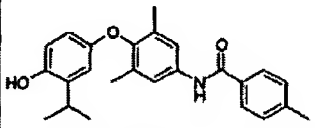
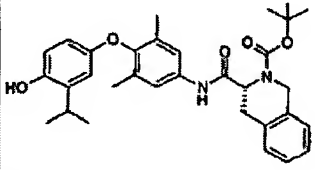
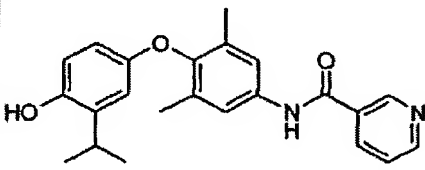
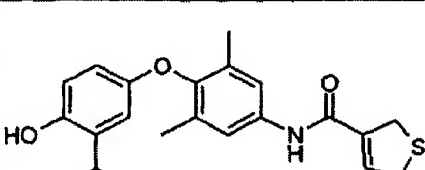
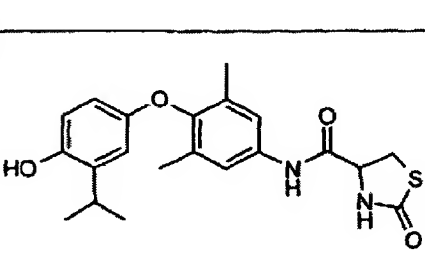
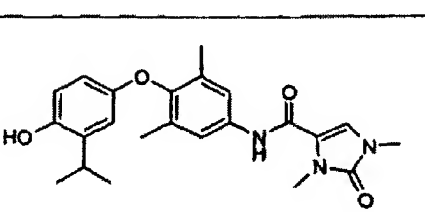
Key: 1 Example No.
 2 Structure
 3 Retention time
 4 Method

① Beispiel-Nr.	② Struktur	③ Retentionszeit	④ Methode
29		5,5	A
30		4,9	A
31		5,2	A
32		4,3	A
33		5,6	A
34		4,6	A

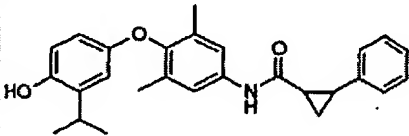
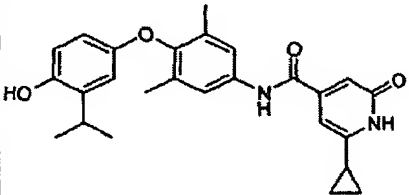
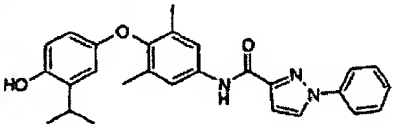
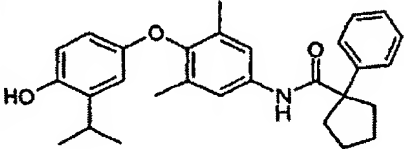
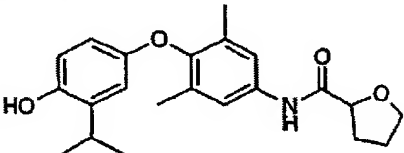
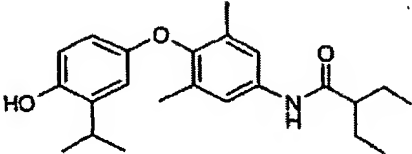
Key: 1 Example No.
 2 Structure
 3 Retention time
 4 Method

① Beispiel-Nr.	② Struktur	③ Retentionszeit	④ Methode
35		4,2	A
36		4,8	A
37		4,9	A
38		5	A
39		5,3	A
40		5,3	A

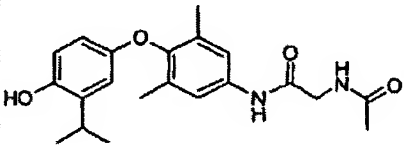
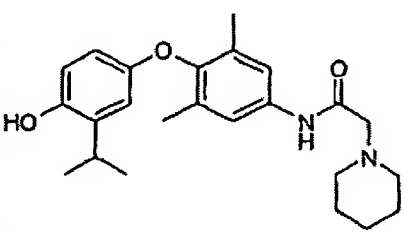
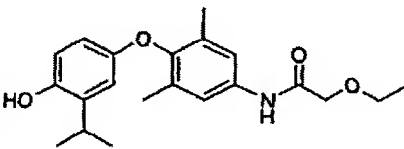
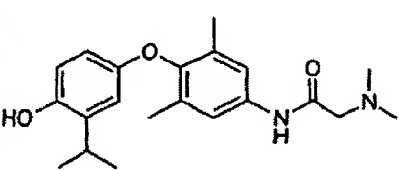
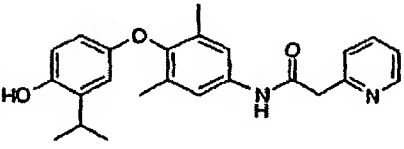
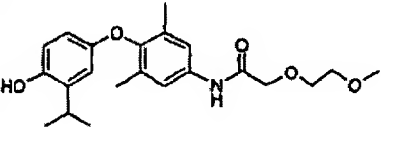
Key: 1 Example No.
 2 Structure
 3 Retention time
 4 Method

① Beispiel-Nr.	② Struktur	③ Retentionszeit	④ Methode
41		4,2	A
42			A
43		5,2	B
44		4,2	B
45		4,7	B
46		4,2	B
47		4,1	B

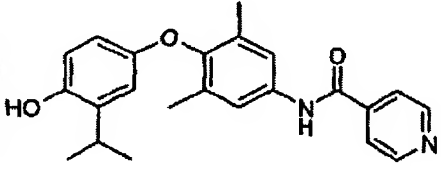
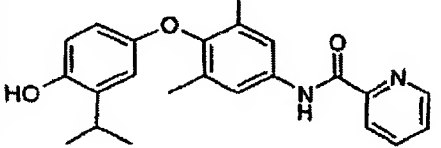
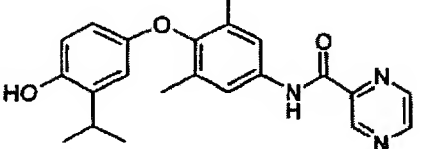
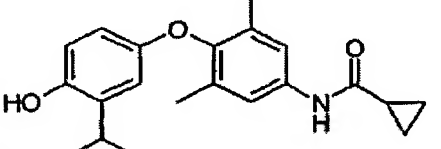
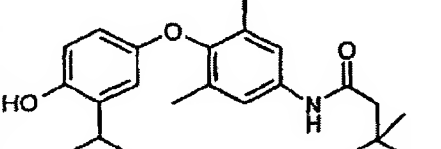
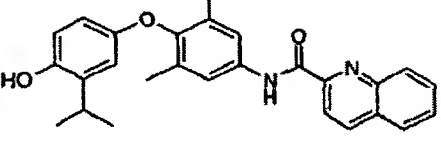
Key: 1 Example No.
 2 Structure
 3 Retention time
 4 Method

① Beispiel-Nr.	② Struktur	③ Retentionszeit	④ Methode
48		5,1	B
49		4,2	B
50		5,2	B
51		5,5	B
52		4,5	B
53		4,9	B

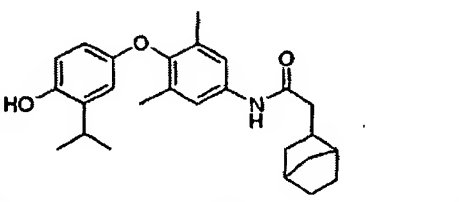
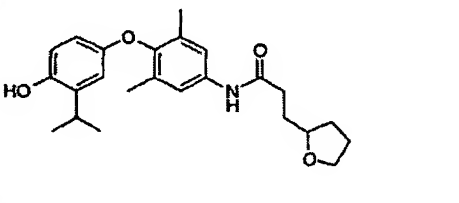
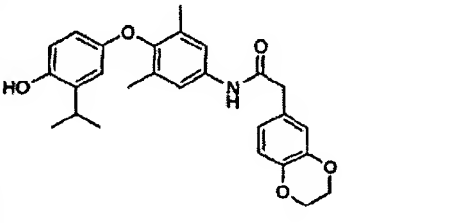
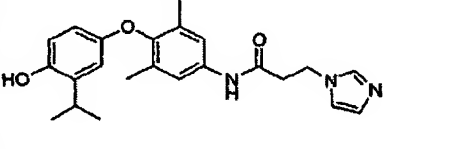
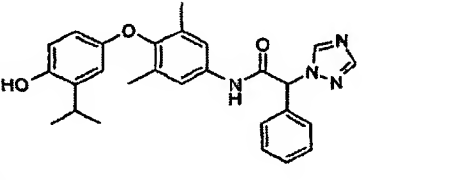
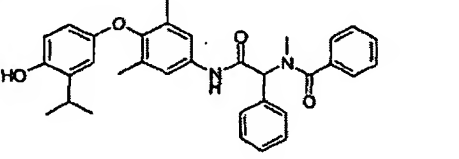
Key: 1 Example No.
 2 Structure
 3 Retention time
 4 Method

① Beispiel-Nr.	② Struktur	③ Retentionszeit	④ Methode
54		3,9	B
55		3,2	B
56		4,6	B
57		3,1	B
58		3,6	B
59		4,4	B

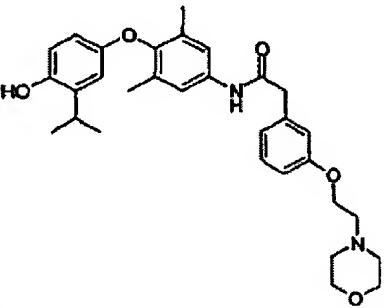
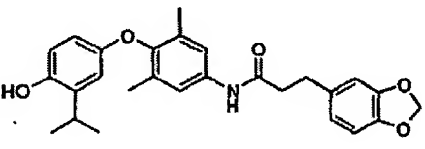
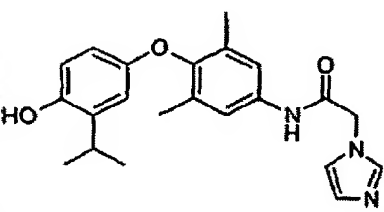
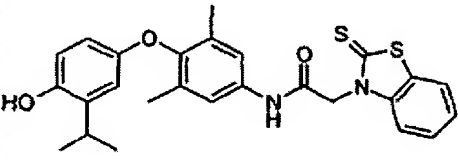
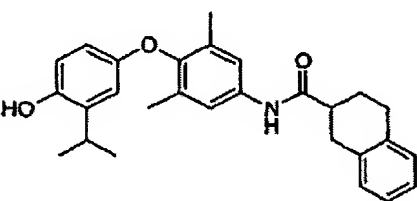
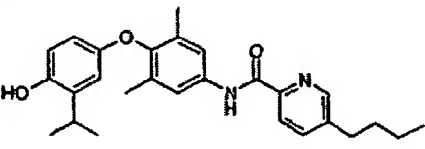
Key: 1 Example No.
 2 Structure
 3 Retention time
 4 Method

① Beispiel-Nr.	② Struktur	③ Retentionszeit	④ Methode
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61		5	B
62		4,6	B
63		4,5	B
64		5	B
65		5,5	B

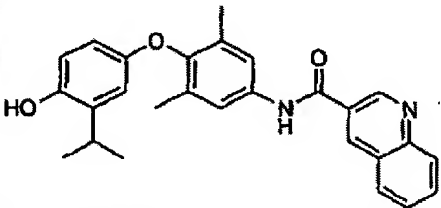
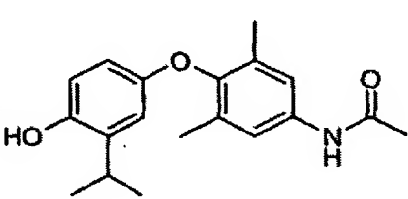
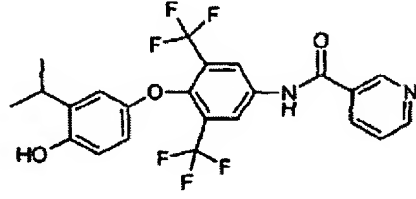
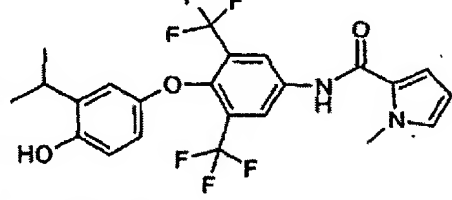
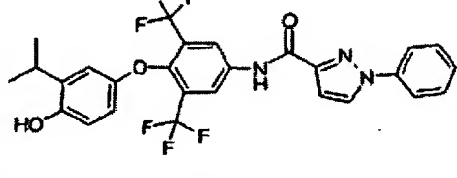
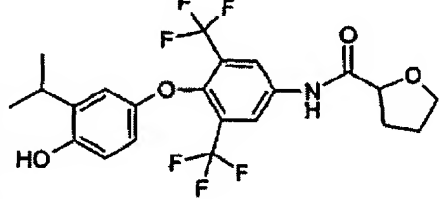
Key: 1 Example No.
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① Beispiel-Nr.	② Struktur	③ Retentionszeit	④ Methode
66		5,2	B
67		4,5	B
68		4,7	B
69		3,1	B
70		4,5	B
71		5,1	B

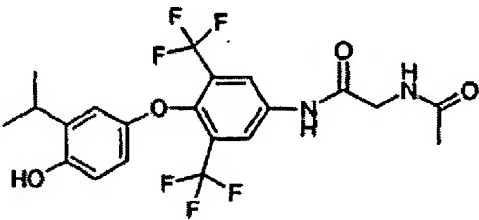
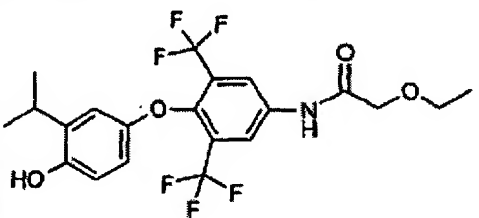
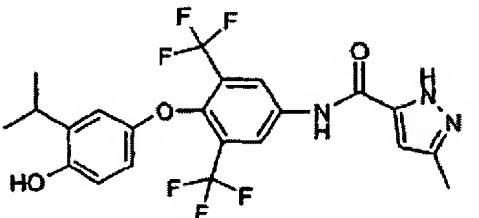
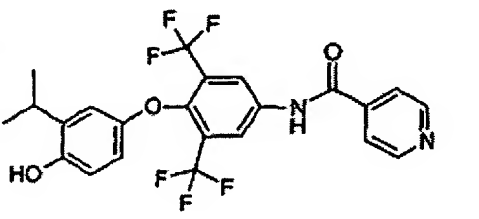
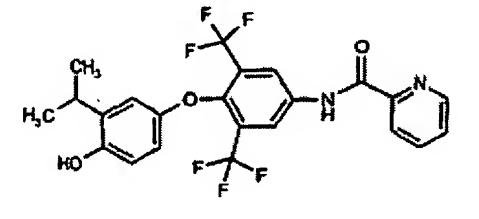
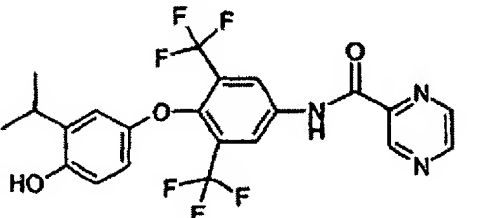
Key: 1 Example No.
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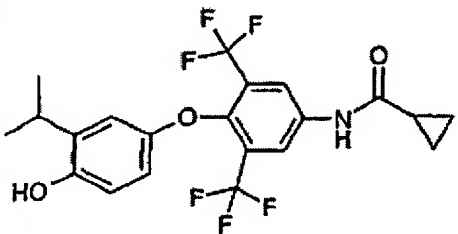
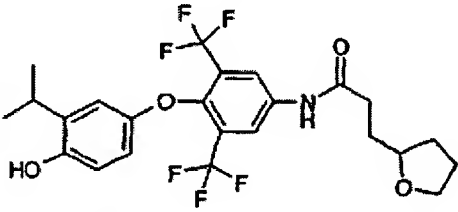
① Beispiel-Nr.	② Struktur	③ Retentionszeit	④ Methode
72		3,3	B
73		4,8	B
74		3,1	B
75		5,2	B
76		5,2	B
77		5,8	B

Key: 1 Example No.
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 3 Retention time
 4 Method

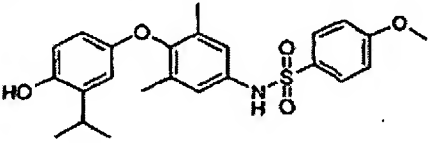
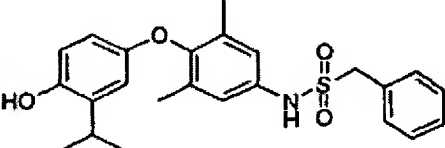
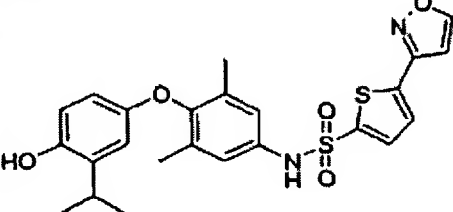
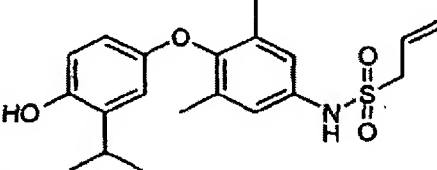
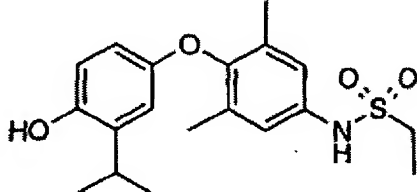
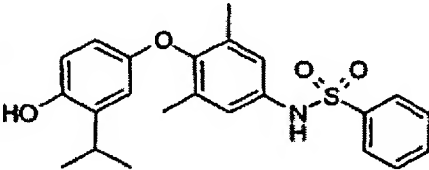
Beispiel-Nr.	Struktur	Retentionszeit	Methode
78		4,7	B
79		4,1	B
80		4,41	A
81		5,19	A
82		5,19	A
83		4,46	A

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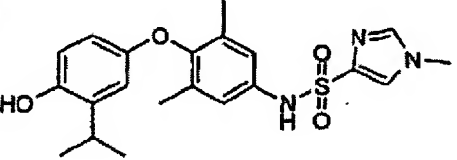
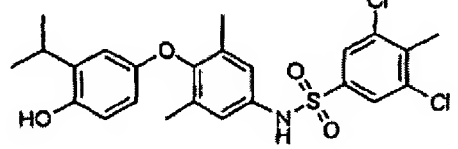
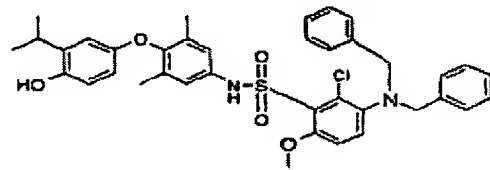
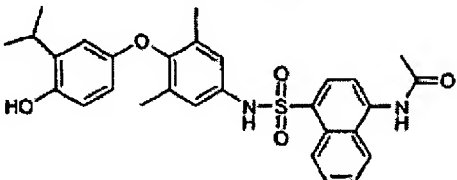
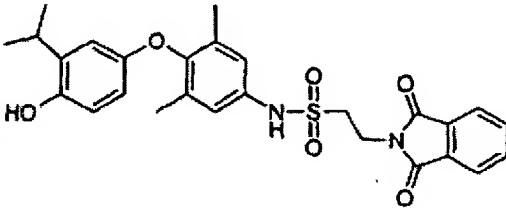
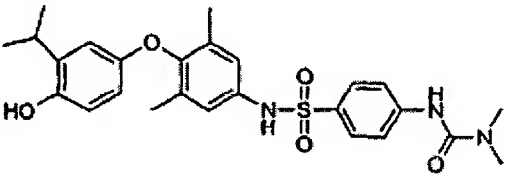
① Beispiel-Nr.	② Struktur	③ Retentionszeit	④ Methode
84		4,01	A
85		4,73	A
86		4,47	A
87		4,38	A
88		4,96	A
89		4,67	A

① Beispiel-Nr.	② Struktur	③ Retentionszeit	④ Methode
90		4,71	A
91		4,68	A

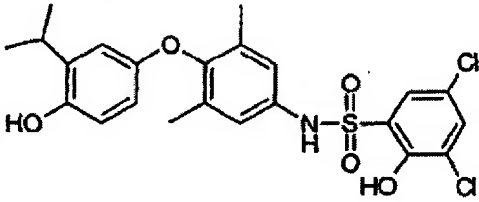
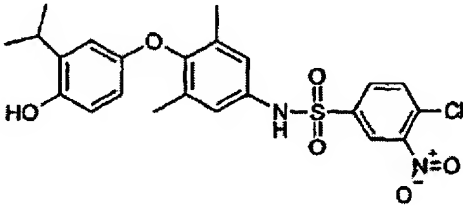
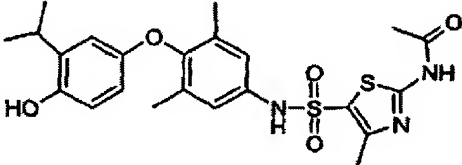
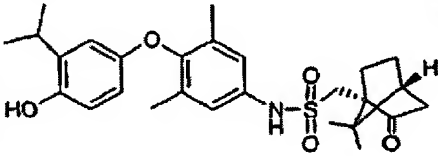
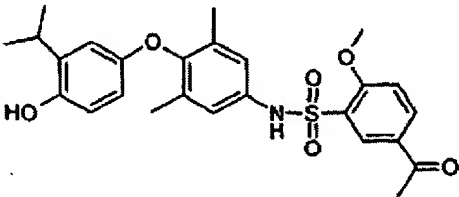
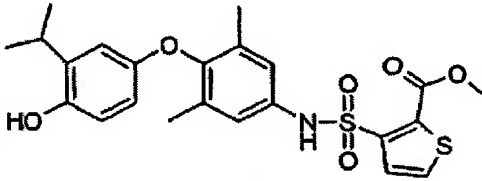
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① Beispiel Nr.	② Struktur	③ Retentionszeit
92		4,8
93		4,9
94		4,9
95		4,7
96		
97		

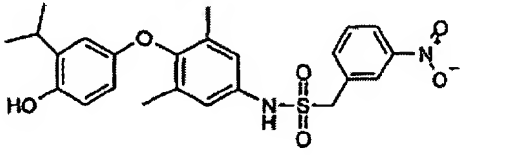
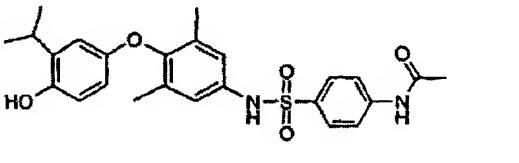
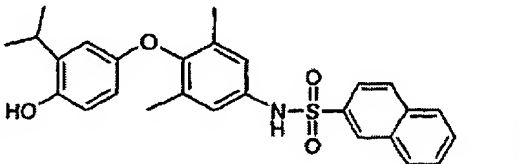
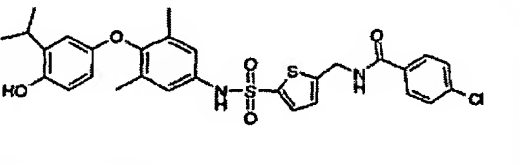
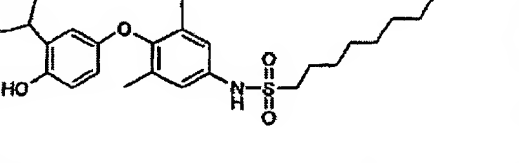
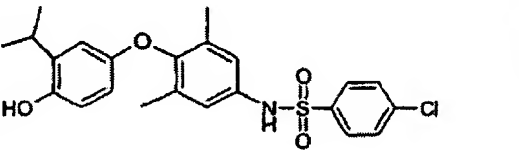
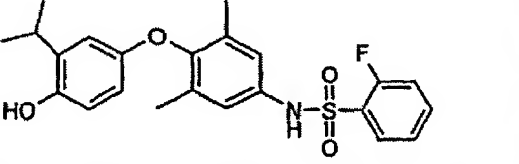
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① Beispiel Nr.	② Struktur	③ Retentionszeit
98		4,23
99		
100		5,29
101		4,23
102		4,45
103		4,13

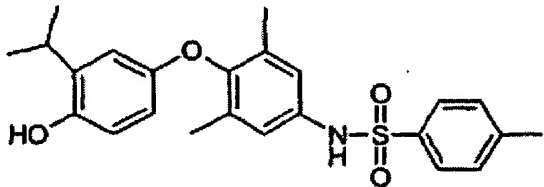
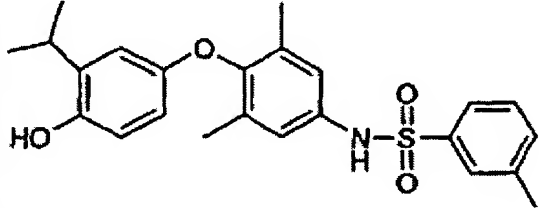
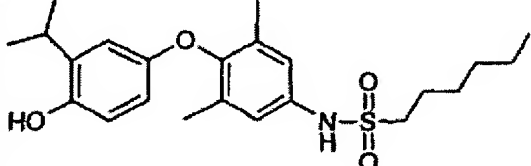
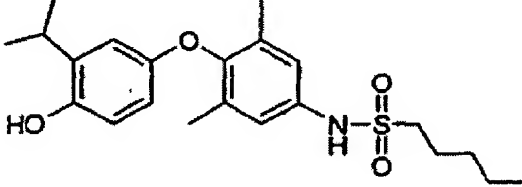
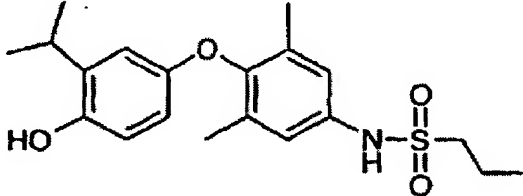
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① Beispiel Nr.	② Struktur	③ Retentionszeit
104		4,84
105		4,77
106		4,14
107		4,73
108		4,3
109		4,63

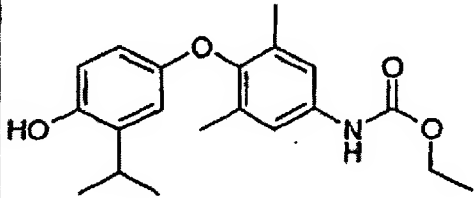
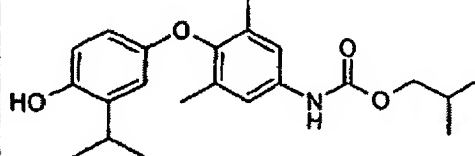
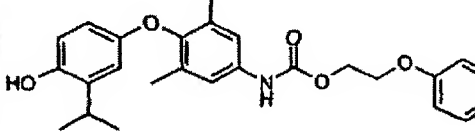
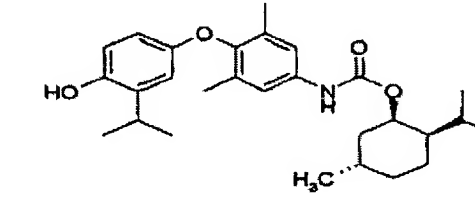
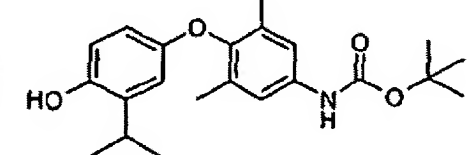
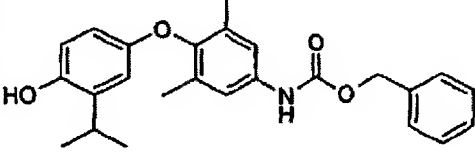
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 3 Retention time

① Beispiel Nr.	② Struktur	③ Retentionszeit
110		4,55
111		4,1
112		4,78
113		4,65
114		5,31
115		4,77
116		4,52

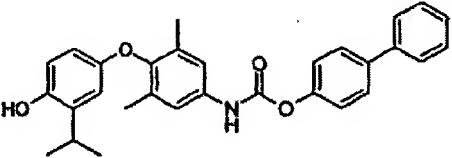
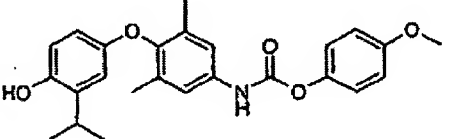
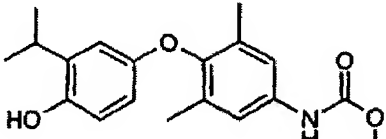
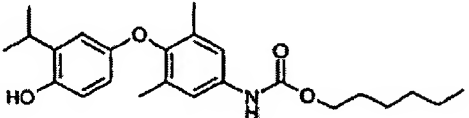
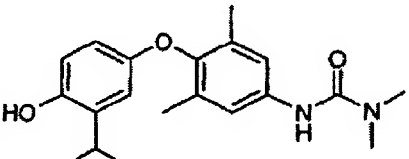
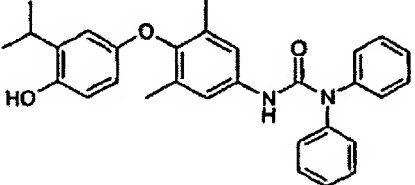
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① Beispiel Nr.	② Struktur	③ Retentionszeit
117		4,65
118		4,66
119		4,95
120		4,76
121		4,42

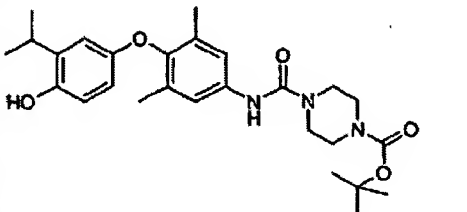
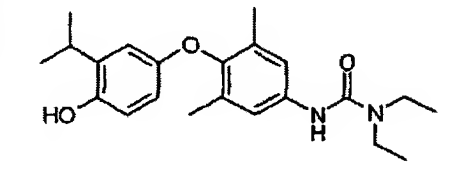
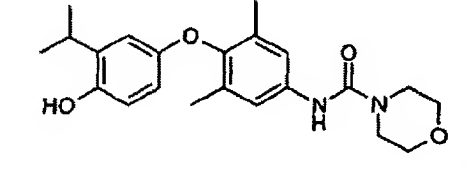
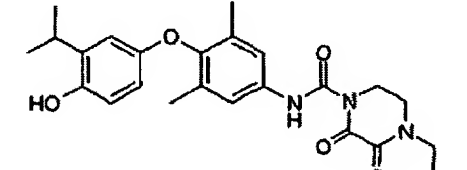
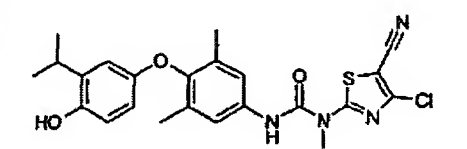
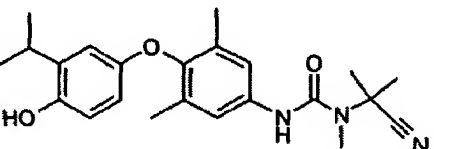
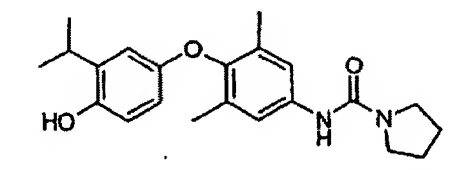
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① Beispiel-Nr.	② Struktur	③ Retentionszeit
122		4,7
123		5,1
124		5
125		6,2
126		
127		

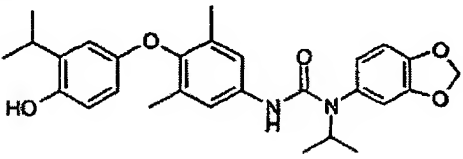
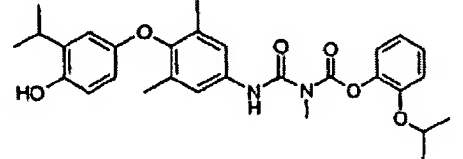
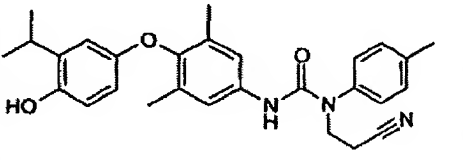
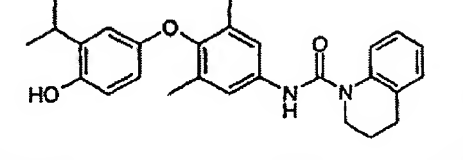
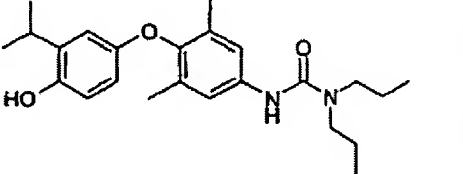
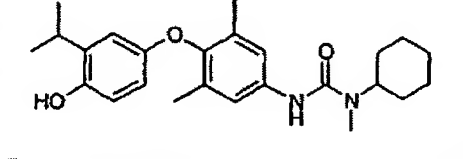
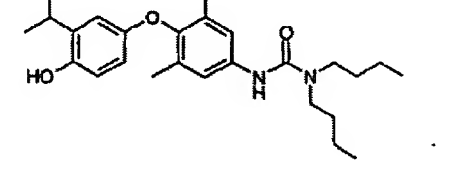
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① Beispiel-Nr.	② Struktur	③ Retentionszeit
128		5,5
129		5
130		4,33
131		5,34
132		
133		5,2

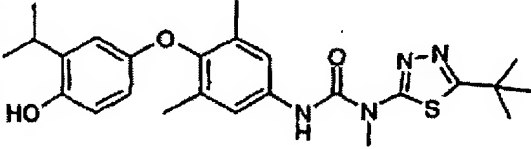
Key: 1 Example No.
 2 Structure
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① Beispiel-Nr.	② Struktur	③ Retentionszeit
134		4,57
135		4,39
136		3,94
137		4,2
138		5
139		2,91
140		4,17

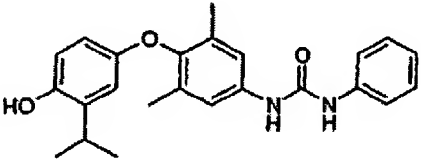
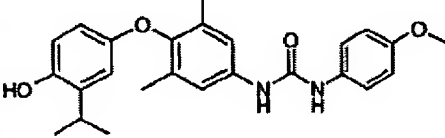
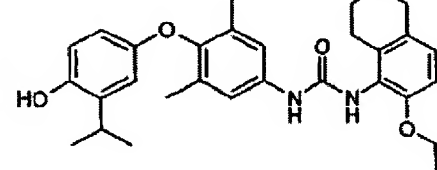
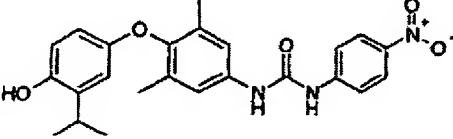
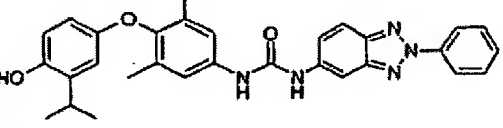
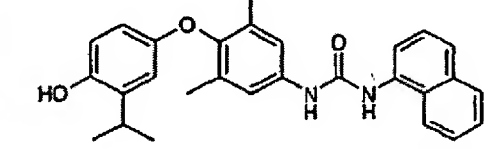
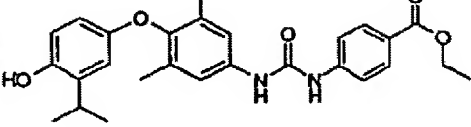
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 2 Structure
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① Beispiel-Nr.	② Struktur	③ Retentionszeit
141		4,9
142		5,48
143		4,73
144		4,9
145		4,82
146		4,82
147		5,21

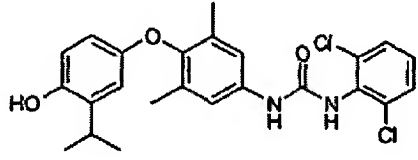
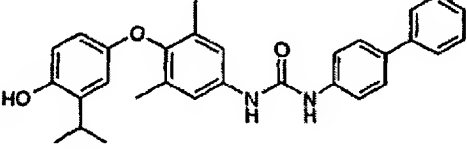
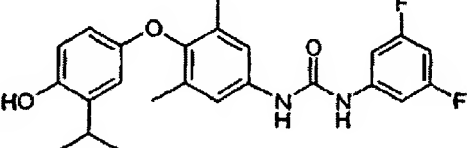
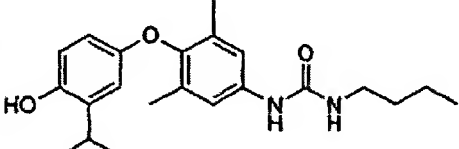
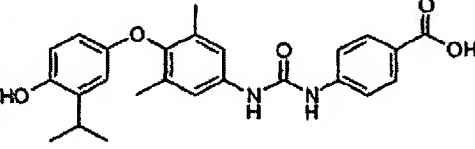
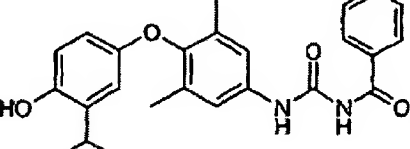
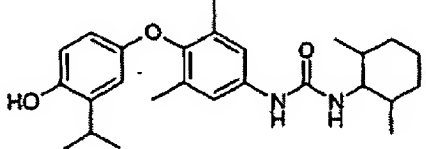
Key: 1 Example No.
 2 Structure
 3 Retention time

① Beispiel-Nr.	② Struktur	③ Retentionszeit
148		4,92

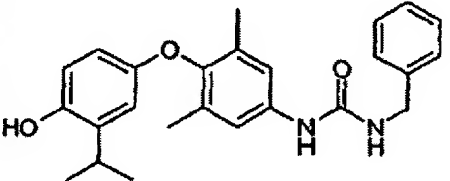
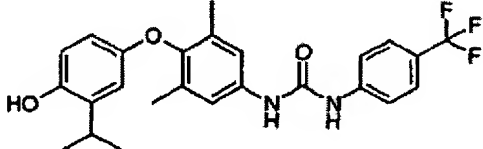
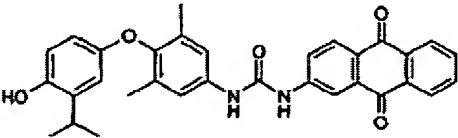
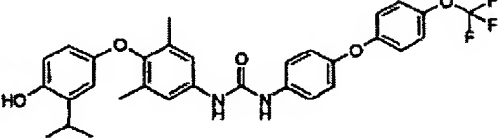
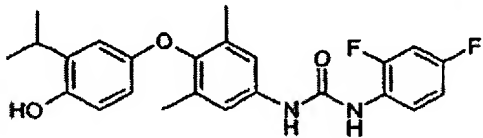
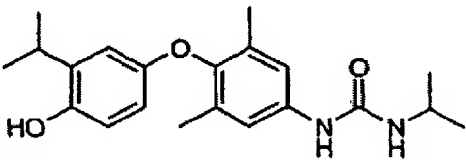
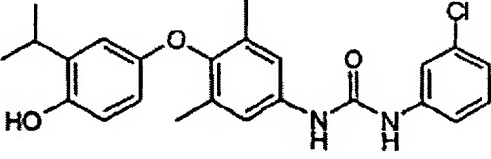
Key: 1 Example No.
 2 Structure
 3 Retention time

① Beispiel Nr.	② Struktur	③ Retentionszeit
149		
150		4,7
151		5,2
152		4,9
153		5,3
154		5
155		5

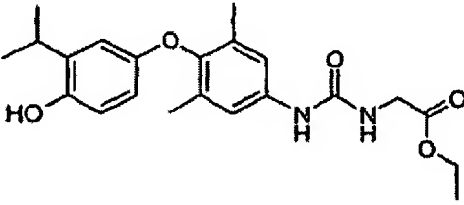
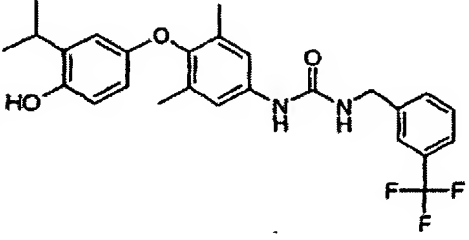
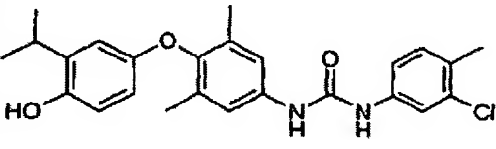
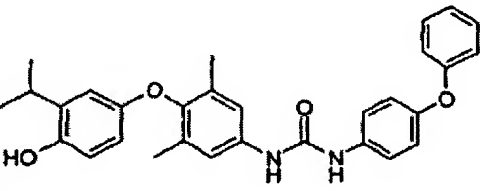
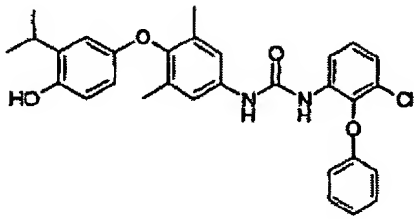
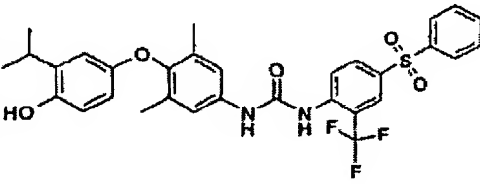
Key: 1 Example No.
 2 Structure
 3 Retention time

① Beispiel Nr.	② Struktur	③ Retentionszeit
156		4,8
157		5,3
157		5,1
158		
159		
160		5
161		5

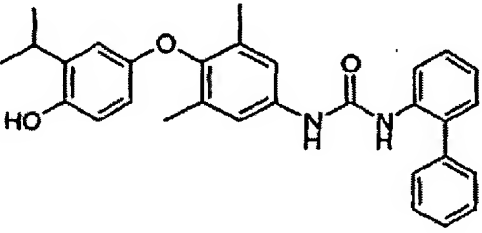
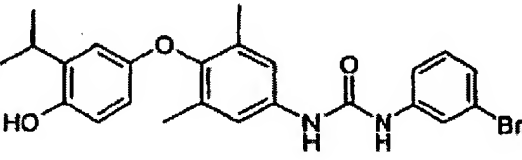
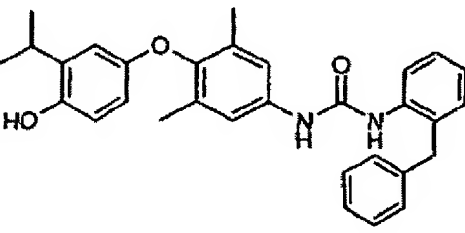
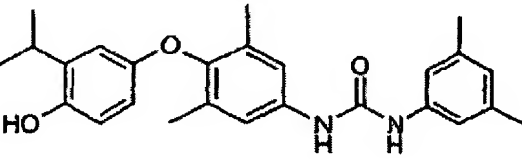
Key: 1 Example No.
 2 Structure
 3 Retention time

① Beispiel Nr.	② Struktur	③ Retentionszeit
162		4,6
163		5,16
164		5,23
165		5,22
166		4,72
167		4,2
168		4,85

Key: 1 Example No.
 2 Structure
 3 Retention time

① Beispiel Nr.	② Struktur	③ Retentionszeit
169		4,11
170		4,71
171		4,99
172		4,99
173		5,28
174		4,97

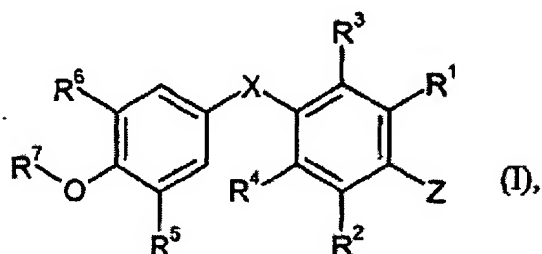
Key: 1 Example No.
 2 Structure
 3 Retention time

① Beispiel Nr.	② Struktur	③ Retentionszeit
175		5
176		4,9
177		4,97
178		4,87

Key: 1 Example No.
 2 Structure
 3 Retention time

Claims

1. Compounds of general formula (I) along with their pharmaceutically acceptable salts, solvates, hydrates and hydrates of the salts



in which

X represents O, S, SO, SO₂, CH₂, CHF, CF₂ or for NR⁸, in which R⁸ represents hydrogen or (C₁-C₄)-alkyl,

R¹ and R² are identical or different and represent hydrogen or (C₁-C₄)-alkyl,

R³ and R⁴ are identical or different and represent hydrogen, halogen, cyano, (C₁-C₆)-alkyl, CF₃, CHF₂, CH₂F, vinyl or (C₃-C₇)-cycloalkyl, whereby at least one of the two substituents is not identical to hydrogen,

R⁵ represents hydrogen, (C₁-C₄)-alkyl or halogen,

R⁶ represents (C₁-C₄)-alkyl, bromine or chlorine or for a group of formula -S-R⁹, -S(O)_n-R¹⁰, -NR¹¹-C(O)-R¹², -CH₂-R¹³ or -M-R¹⁴, in which

R⁹ represents (C₁-C₁₀)-alkyl, (C₃-C₈)-cycloalkyl, (C₂-C₆)-alkenyl, (C₆-C₁₀)-aryl, (C₆-C₁₀)-arylmethyl, or for a saturated, partially unsaturated or aromatic 5- to 10-membered heterocycle with up to four identical or different heteroatoms from the series N, O and/or S, whereby the aforementioned residues are optionally substituted by one, two or three identical or different substituents selected from the group comprising halogen, nitro, trifluoromethyl, hydroxy, oxo, cyano, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, carboxyl and (C₁-C₄)-alkoxycarbonyl,

n represents the number 1 or 2,

R¹⁰ represents OR¹⁵, NR¹⁶R¹⁷, (C₁-C₁₀)-alkyl, (C₃-C₈)-cycloalkyl, (C₂-C₆)-alkenyl, (C₆-C₁₀)-aryl, (C₆-C₁₀)-arylmethyl or for a saturated, partially unsaturated or aromatic 5- to 10-membered heterocycle with up to four identical or different heteroatoms from the series N, O and/or S, whereby the aforementioned residues are optionally substituted by one, two or three identical or different substituents selected from the group comprising halogen, hydroxy, oxo, cyano,

nitro, amino, $\text{NR}^{18}\text{R}^{19}$, trifluoromethyl, $(\text{C}_1\text{-C}_6)\text{-alkyl}$, $(\text{C}_1\text{-C}_6)\text{-alkoxy}$ that has optionally been substituted by R^{20} , $(\text{C}_3\text{-C}_8)\text{-cycloalkyl}$, $(\text{C}_6\text{-C}_{10})\text{-aryl}$ that in turn has optionally been substituted by halogen, $(\text{C}_1\text{-C}_4)\text{-alkyl}$, $(\text{C}_1\text{-C}_4)\text{-alkoxy}$, trifluoromethyl, nitro or cyano, $-\text{O}-\text{C}(\text{O})-\text{R}^{21}$, $-\text{O}-\text{C}(\text{O})-\text{R}^{22}$, $-\text{C}(\text{O})-\text{NR}^{23}\text{R}^{24}$, $-\text{SO}_2-\text{NR}^{25}\text{R}^{26}$, $-\text{NH}-\text{C}(\text{O})-\text{R}^{27}$ and $-\text{NH}-\text{C}(\text{O})-\text{OR}^{28}$, whereby

R^{15} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} and R^{28} are identical or different and in each case represent hydrogen, phenyl, benzyl, $(\text{C}_1\text{-C}_6)\text{-alkyl}$ or $(\text{C}_3\text{-C}_8)\text{-cycloalkyl}$ that are in turn optionally substituted singly or multiply, identically or differently, by halogen, hydroxy, amino, carboxyl, $(\text{C}_1\text{-C}_4)\text{-alkoxy}$, $(\text{C}_1\text{-C}_4)\text{-alkoxycarbonyl}$, $(\text{C}_1\text{-C}_4)\text{-alkoxycarbonylamino}$, $(\text{C}_1\text{-C}_5)\text{-alkanoyloxy}$, a heterocycle or by phenyl that in turn is optionally substituted by halogen or hydroxy,

and

R^{16} and R^{17} are identical or different and, independently of one another, represent hydrogen, straight-chain or branched $(\text{C}_1\text{-C}_6)\text{-alkyl}$ that can be substituted singly or multiply, identically or differently, by mono- $(\text{C}_1\text{-C}_6)\text{-alkylamino}$, di- $(\text{C}_1\text{-C}_6)\text{-alkylamino}$, $(\text{C}_1\text{-C}_4)\text{-alkoxy}$, $(\text{C}_1\text{-C}_6)\text{-alkoxycarbonyl}$, carboxyl, pyridyl or $(\text{C}_6\text{-C}_{10})\text{-aryl}$, whereby the latter in turn is optionally substituted by halogen, trifluoromethyl, $(\text{C}_1\text{-C}_6)\text{-alkyl}$ or $(\text{C}_1\text{-C}_6)\text{-alkoxy}$, or $(\text{C}_6\text{-C}_{10})\text{-aryl}$ that is optionally substituted by halogen, trifluoromethyl, $(\text{C}_1\text{-C}_6)\text{-alkyl}$ or $(\text{C}_1\text{-C}_6)\text{-alkoxy}$, or $(\text{C}_3\text{-C}_8)\text{-cycloalkyl}$, or a 5- to 7-membered heterocycle that contains two nitrogen atoms, whereby the cycloalkyl group and the heterocycle are in turn optionally substituted by $(\text{C}_1\text{-C}_4)\text{-alkyl}$,

or

R^{16} and R^{17} together with the nitrogen atom to which they are bonded form a 5- to 7-membered, saturated, and optionally benzo-annellated, heterocycle that can contain up to two further heteroatoms from the series N, O and/or S and that can be substituted by amino, $(\text{C}_1\text{-C}_6)\text{-alkyl}$, $(\text{C}_1\text{-C}_4)\text{-alkoxycarbonyl}$, $(\text{C}_1\text{-C}_4)\text{-alkoxycarbonylamino}$ or phenyl,

R^{11} represents hydrogen, straight-chain or branched $(\text{C}_1\text{-C}_6)\text{-alkyl}$ that can be substituted singly or multiply, identically or differently, by mono- $(\text{C}_1\text{-C}_6)\text{-alkylamino}$, di- $(\text{C}_1\text{-C}_6)\text{-alkylamino}$, $(\text{C}_1\text{-C}_4)\text{-alkoxy}$, $(\text{C}_1\text{-C}_6)\text{-alkoxycarbonyl}$, carboxyl, pyridyl or $(\text{C}_6\text{-C}_{10})\text{-aryl}$, whereby the latter in turn is optionally substituted by halogen, trifluoromethyl, $(\text{C}_1\text{-C}_6)\text{-alkyl}$ or $(\text{C}_1\text{-C}_6)\text{-alkoxy}$, or

(C₃-C₈)-cycloalkyl, or a 5- to 7-membered heterocycle that contains two nitrogen atoms, whereby the cycloalkyl group and the heterocycle are in turn optionally substituted by (C₁-C₄)-alkyl,

R¹² represents straight-chain or branched (C₁-C₁₅)-alkyl that can be substituted by (C₃-C₈)-cycloalkyl, (C₁-C₄)-alkoxy, phenyl, phenoxy or benzyloxy, whereby the designated aromatic groups in turn can in each case be substituted identically or differently up to three times by halogen, (C₁-C₆)-alkyl or (C₁-C₄)-alkoxy,

or (C₃-C₈)-cycloalkyl that can be substituted by (C₁-C₄)-alkoxy or phenyl,

or (C₆-C₁₀)-aryl that can be substituted identically or differently up to three times by (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, halogen, cyano, amino, trifluoromethyl or phenyl,

or

a 5-6 membered saturated or aromatic heterocycle, which has optionally been benzo-annellated, with up to two heteroatoms from the series N, O and/or S,

or

it signifies a group of formula -OR²⁹ or -NR³⁰R³¹

in which

R²⁹ represents straight-chain or branched (C₁-C₆)-alkyl

and

R³⁰ and R³¹ are identical or different and, independently of one another, stand for hydrogen, straight-chain or branched (C₁-C₁₂)-alkyl that can be substituted by aminocarbonyl, a group of formula -NR³²R³³, a 5-6 membered heteroaryl group that contains up to 3 heteroatoms selected from the group comprising N, O and/or S or that can be substituted by phenyl, whereby this phenyl group is optionally substituted identically or differently up to two times by halogen, (C₁-C₄)-alkyl, trifluoromethyl or (C₁-C₄)-alkoxy,

or (C₃-C₈)-cycloalkyl that can be substituted by (C₁-C₄)-alkyl,

or (C₆-C₁₀)-aryl that can be substituted identically or differently up to three times by halogen, (C₁-C₄)-alkyl, trifluoromethyl, (C₁-C₄)-alkoxy, amino, phenyl or phenoxy,

or
for a 5- to 7-membered saturated or unsaturated heterocycle that contains one or two nitrogen atoms and that is optionally substituted by (C₁-C₄)-alkyl or an oxo group,

whereby

R³² and R³³ are identical or different and, independently of one another, represent hydrogen, (C₁-C₆)-alkyl, phenyl or (C₆-C₁₀)-arylsulfonyl,
or,

jointly with the nitrogen atom to which they are bonded, they form a 3-7 membered saturated heterocycle that optionally contains up to two further heteroatoms from the series N, O and/or S,

or

R^{30} and R^{31} , jointly with the nitrogen atom to which they are bonded, form a 4-7 membered saturated heterocycle that can contain up to two further heteroatoms from the series N, O and/or S and that can be substituted by amino, (C₁-C₆)-alkyl, (C₁-C₄)-alkanoyl, aminocarbonyl,

(C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkoxycarbonylamino, phenyl or pyridyl,

R^{13} represents a saturated, partially unsaturated or aromatic 5- to 10-membered heterocycle with up to three identical or different heteroatoms from the series N, O and/or S and that is optionally substituted by one, two or three identical or different substituents selected from the group (C₁-C₄)-alkyl, hydroxy, oxo, (C₁-C₄)-alkoxy, halogen, cyano, carboxyl and (C₁-C₄)-alkoxycarbonyl,

or

R^{13} represents the group $-NR^{34}R^{35}$ in which

R^{34} and R^{35} are identical or different and represent hydrogen, (C₁-C₈)-alkyl that can be substituted by (C₆-C₁₀)-aryl, or (C₃-C₈)-cycloalkyl, (C₆-C₁₀)-aryl or for a 5-6 membered heteroaryl group with up to three identical or different heteroatoms from the series N, O and/or S, whereby the aryl and heteroaryl groups are in turn optionally substituted in each case identically or differently either one or two times by hydroxy, amino, cyano, halogen, trifluoromethyl, (C₁-C₄)-alkyl, (C₁-C₄)-alkoxy, carboxyl, (C₁-C₄)-alkoxycarbonyl or mono-(C₁-C₄)-alkylaminocarbonyl or di-(C₁-C₄)-alkylaminocarbonyl,

M represents C=O, CH(OH), CHF or CF₂,

and

R^{14} has the meaning indicated above for R^{10} ,

R^7 represents hydrogen, (C₁-C₄)-alkyl or (C₁-C₄)-alkanoyl

and

Z represents a group $NH-SO_2-R^{36}$, $NH-CO_2-R^{37}$, $NH-CO-NR^{38}R^{39}$ or $NH-CO-R^{40}$ in which

R^{36} , R^{37} , R^{38} , R^{39} and R^{40} in each case represent an unsubstituted or

substituted alkyl, alkenyl, cycloalkyl, aryl, heterocyclyl or heteroaryl group.

2. Compounds of general formula (I) in accordance with Claim 1 along with their pharmaceutically acceptable salts, solvates, hydrates and hydrates of the salts

in which

X represents O, S, CH₂ or CF₂,

R^1 and R^2 are identical or different and represent hydrogen or methyl,

R^3 and R^4 are identical or different and represent hydrogen, halogen, (C_1-C_4) -alkyl, CF_3 , CHF_2 , CH_2F , vinyl or (C_3-C_5) -cycloalkyl, whereby at least one of the two substituents is not identical to hydrogen,

R^5 represents hydrogen, (C_1-C_3) -alkyl, fluorine, chlorine or bromine,

R^6 represents (C_1-C_3) -alkyl or a group of formula $-S(O)_2-R^{10}$, $-NR^{11}-C(O)-R^{12}$, $-CH_2-R^{13}$ or $-M-R^{14}$, in which

R^{10} represents $NR^{16}R^{17}$, (C_1-C_8) -alkyl, (C_5-C_7) -cycloalkyl, phenyl, benzyl or a saturated, partially unsaturated or aromatic 5- to 10-membered heterocycle with up to three identical or different heteroatoms from the series N, O and/or S, whereby the aforementioned residues are optionally substituted by one, two or three identical or different substituents selected from the group comprising halogen, hydroxy, oxo, cyano, nitro, amino, dimethylamino, trifluoromethyl, (C_1-C_4) -alkyl, (C_1-C_4) -alkoxy, (C_3-C_6) -cycloalkyl, phenyl that in turn has optionally been substituted by halogen, (C_1-C_4) -alkyl, (C_1-C_4) -alkoxy, trifluoromethyl, nitro or cyano, $-C(O)-R^{22}$, $-C(O)-NR^{23}R^{24}$, $-SO_2-NR^{25}R^{26}$, $-NH-C(O)-R^{27}$ and $-NH-C(O)-OR^{28}$, whereby

R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} and R^{28} are identical or different and in each case represent hydrogen, phenyl, benzyl, (C_1-C_4) -alkyl or (C_5-C_7) -cycloalkyl that are in turn optionally substituted singly or multiply, identically or differently, by halogen, hydroxy, amino, carboxyl, (C_1-C_4) -alkoxy, (C_1-C_4) -alkoxycarbonyl, (C_1-C_4) -alkoxycarbonylamino or (C_1-C_5) -alkanoyloxy,

and

R^{16} and R^{17} are identical or different and, independently of one another, represent hydrogen, straight-chain or branched (C_1-C_6) -alkyl that can be substituted singly or multiply, identically or differently, by (C_1-C_4) -alkoxy, (C_1-C_4) -alkoxycarbonyl, carboxyl, pyridyl or phenyl, whereby the latter in turn is optionally substituted by halogen, trifluoromethyl, (C_1-C_4) -alkyl or (C_1-C_4) -alkoxy, or phenyl that is optionally substituted by halogen, trifluoromethyl, (C_1-C_4) -alkyl or (C_1-C_4) -alkoxy, or (C_5-C_7) -cycloalkyl, or a 5- to 7-membered heterocycle that contains up to two nitrogen atoms, whereby the cycloalkyl group and the heterocycle are in turn optionally substituted by (C_1-C_4) -alkyl,

or

R^{16} and R^{17} together with the nitrogen atom to which they are bonded form a 5- to 7-membered saturated heterocycle that can contain up to two further heteroatoms from the series N, O and/or S and that can be substituted by amino, (C₁-C₄)-alkyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkoxycarbonylamino or phenyl,

R^{11} represents hydrogen, straight-chain or branched (C₁-C₄)-alkyl, benzyl, (C₃-C₇)-cycloalkyl or for a 5- to 7-membered heterocycle that contains one or two nitrogen atoms, whereby the cycloalkyl group and the heterocycle are optionally substituted by (C₁-C₄)-alkyl,

R^{12} represents straight-chain or branched (C₁-C₈)-alkyl that can be substituted by (C₃-C₇)-cycloalkyl, (C₁-C₄)-alkoxy, phenyl, phenoxy or benzyloxy, whereby the designated aromatic compounds can in turn, in each case, be substituted identically or differently up to three times by halogen, (C₁-C₄)-alkyl or (C₁-C₄)-alkoxy,

or

phenyl that can be substituted identically or differently up to three times by (C₁-C₄)-alkyl, (C₁-C₄)-alkoxy, halogen, cyano, amino or trifluoromethyl,

or

it signifies a group of formula $-OR^{29}$ or $-NR^{30}R^{31}$

in which

R^{29} represents straight-chain or branched (C₁-C₄)-alkyl

and

R^{30} and R^{31} are identical or different and, independently of one another, represent

hydrogen, a straight-chain or branched (C₁-C₈)-alkyl that can be substituted by phenyl that in turn is optionally substituted identically or differently up to two times by halogen, (C₁-C₄)-alkyl, trifluoromethyl or (C₁-C₄)-alkoxy, or (C₃-C₇)-cycloalkyl that can be substituted by (C₁-C₄)-alkyl,

or

phenyl that can be substituted identically or differently up to three times by halogen, (C₁-C₄)-alkyl, trifluoromethyl, (C₁-C₄)-alkoxy or amino,

or

R^{30} and R^{31} jointly with the nitrogen atom to which they are bonded form a 5- to 7-membered saturated heterocycle that can contain up to two further heteroatoms from the series N, O and/or S and that can be substituted by amino, (C₁-C₄)-alkyl, (C₁-C₄)-alkanoyl, aminocarbonyl, (C₁-C₄)-alkoxycarbonyl, (C₁-C₄)-alkoxycarbonylamino or phenyl,

R^{13} represents a saturated, partially unsaturated or aromatic 5-6 membered heterocycle with up to three identical or different heteroatoms from the series N, O and/or S and that is optionally substituted by one, two or three identical or different substituents selected from the group (C₁-C₄)-alkyl, hydroxy, oxo, (C₁-C₄)-alkoxy, halogen, cyano, carboxyl and (C₁-C₄)-alkoxycarbonyl,

or

the group $-NR^{34}R^{35}$ in which

R^{34} and R^{35} are identical or different and represent hydrogen, (C₁-C₆)-alkyl that can be substituted by phenyl, or (C₅-C₇)-cycloalkyl, phenyl or for a 5-6 membered heteroaryl group with up to three identical or different heteroatoms from the series N, O and/or S, whereby the phenyl and heteroaryl groups are in turn optionally substituted in each case identically or differently either one or two times by hydroxy, amino, cyano, halogen, (C₁-C₄)-alkyl, trifluoromethyl, (C₁-C₄)-alkoxy, carboxyl or (C₁-C₄)-alkoxycarbonyl,

M represents C=O, CH(OH), or CF₂,

and

R^{14} has the meaning indicated above for R^{10} , and

R^7 represents hydrogen, methyl or acetyl.

3. Compounds of general formula (I) in accordance with Claim 1, along with their pharmaceutically acceptable salts, solvates, hydrates and hydrates of the salts are especially preferred:

in which

X represents O, S or CH₂,

R^1 and R^2 represent hydrogen,

R^3 and R^4 are identical or different and represent methyl, ethyl, propyl, isopropyl, cyclopropyl, trifluoromethyl, chlorine or bromine,

R^5 represents hydrogen,

R^6 represents (C₁-C₃)-alkyl or for a group of formula $-S(O)_2-R^{10}$, $-NH-C(O)-R^{12}$, $-CH_2-R^{13}$, $-C(O)-R^{14}$ or $-CH(OH)-R^{41}$, in which

R^{10} represents phenyl or a 5-6 membered heteroaryl group with up to three identical or different heteroatoms from the series N, O and/or S that are optionally substituted singly or doubly, identically or differently, by fluorine, chlorine, bromine, hydroxy, cyano, trifluoromethyl, (C₁-C₄)-alkyl, (C₁-C₄)-alkoxy, carboxyl or (C₁-C₄)-alkoxycarbonyl,

or

the group $-NR^{16}R^{17}$, in which

R^{16} and R^{17} together with the nitrogen atom to which they are bonded form a 5-6 membered saturated heterocycle that can contain an additional heteroatom from the series N, O and/or S and can be substituted by (C₁-C₄)-alkyl,

R^{12} represents straight-chain or branched (C₁-C₆)-alkyl that is optionally substituted by phenoxy or benzyloxy,

R^{13} represents a 5-6 membered heteroaryl group with up to three identical or different heteroatoms from the series N, O and/or S and that is optionally substituted by one or two identical or different substituents selected from the group (C₁-C₄)-alkyl, hydroxy, (C₁-C₄)-alkoxy, fluorine, chlorine, bromine, cyano, carboxyl and (C₁-C₄)-alkoxycarbonyl, or it represents the group $-NR^{34}R^{35}$ in which

R^{34} represents (C₁-C₆)-alkyl or (C₅-C₇)-cycloalkyl,

and

R^{35} represents benzyl that is optionally substituted in the phenyl ring by hydroxy, (C₁-C₄)-alkoxy, (C₁-C₄)-alkyl, trifluoromethyl, fluorine, chlorine or cyano,

R^{14} represents a group of formula $-NR^{42}R^{43}$ in which

R^{42} represents hydrogen, (C₁-C₆)-alkyl or (C₅-C₇)-cycloalkyl,

R^{43} represents hydrogen or (C₁-C₄)-alkyl that can be substituted by phenyl,

or

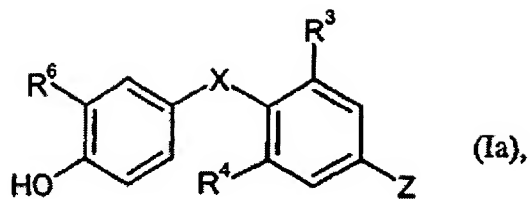
R^{42} and R^{43} together with the nitrogen atom to which they are bonded form a 5-6 membered saturated heterocycle that can contain one additional heteroatom from the series N, O and/or S and that can be substituted by (C₁-C₄)-alkyl,

and

R^{41} represents phenyl that is optionally substituted singly or doubly, identically or differently, by fluorine, chlorine, bromine, (C₁-C₄)-alkyl, (C₁-C₄)-alkoxy, cyano, trifluoromethyl or (C₁-C₄)-alkoxycarbonyl,

R^7 represents hydrogen.

4. Compounds of formula (Ia)



in which

X represents CH_2 or, in particular, O,

R^3 and R^4 are identical or different and represent bromine, trifluoromethyl, ethyl, cyclopropyl and, in particular, for methyl or chlorine,

and

R^6 represents isopropyl,

and

Z represents a group $\text{NH-SO}_2\text{-R}^{36}$, $\text{NH-CO}_2\text{-R}^{37}$, $\text{NH-CO-NR}^{38}\text{R}^{39}$ or NH-CO-R^{40} in which R^{36} , R^{37} , R^{38} , R^{39} and R^{40} in each case represent an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, heterocyclyl or heteroaryl group.

5. Compounds of formulas (I) or (Ia) in accordance with one of the Claims 1-4 in which

R^{36} represents unsubstituted or substituted alkyl with 1-10 carbon atoms or alkenyl with 2-4 carbon atoms or unsubstituted or substituted phenyl, naphthyl, benzyl, thiophenyl, imidazolyl, or thiazolyl,

R^{37} represents an unsubstituted or substituted alkyl group with 1-10 carbon atoms, or an unsubstituted or substituted cycloalkyl group with 5-8 carbon atoms, or phenyl or benzyl that is, in each case, unsubstituted or substituted,

R^{38} represents hydrogen, unsubstituted or substituted alkyl with 1-6 carbon atoms, or it represents phenyl that has optionally been substituted by alkyl,

R^{39} represents unsubstituted or substituted alkyl with 1-8 carbon atoms or it represents either unsubstituted or substituted phenyl, benzyl, naphthyl, anthraquinonyl, tetrahydronaphthyl, tetrahydroquinoline, benzotriazolyl, benzodioxolanyl, thiadiazolyl, pyrazanyl, morpholinyl, thiazolyl or pyrrolidinyl, or it represents either unsubstituted or substituted phenoxycarbonyl or phenylcarbonyl that is in each case, or it represents unsubstituted or substituted cycloalkyl with 4-8 carbon atoms.

R^{38} and R^{39} together with the nitrogen atom to which they are bonded also form an unsubstituted or substituted, saturated or unsaturated 5- to 7-membered heterocycle with up to 3 heteroatoms from the series S, N and/or O.

R⁴⁰ represents unsubstituted or substituted alkyl with 1-8 carbon atoms, or it represents unsubstituted or substituted alkylene with 2-4 carbon atoms, or it represents an unsubstituted or substituted residue selected from the following: cycloalkyl with 3-8 carbon atoms, aryl or heteroaryl, particularly such as benzyl, phenyl, furanyl, thiophenyl, isooxazolyl, pyridyl, imidazolyl, pyrazinyl, quinolinyl, pyrazolyl, triazolyl, pyrrolyl, heterocyclyl with 5-8 ring atoms and at least one O, N or S atom such as in particular tetrahydrofuranyl, tetrahydroisoquinoline, dihydrothiophene, thiazolidinyl, imidazolinyl, dihydropyridinyl, piperidinyl, or it represents phenylalkoxy.

6. Compounds of formulas (I) or (Ia) in accordance with one of the Claims 1-4 in which

R³⁶ represents alkyl with 1-8 carbon atoms that has optionally been substituted by phthalimido or oxo, or vinyl or allyl, or phenyl, unsubstituted or substituted by C₁-C₄-alkoxy; C₁-C₄-alkyl, halogen, ureylene, hydroxy, nitro, alkylcarbonyl, alkylcarbonylamino and/or bis-benzylamino, or benzyl, unsubstituted or substituted by nitro; or thiophenyl that has optionally been substituted by alkoxycarbonyl, oxazolyl or the group -CH₂-NH-CO-chlorophenol, or imidazolyl that has optionally been substituted by alkyl, or thiazolyl or naphthyl that has, in each case, optionally been substituted by alkylcarbonylamino,

R³⁷ represents alkyl with 1-10 carbon atoms that has optionally been substituted by phenoxy, or phenyl or benzyl that is, in each case, unsubstituted or substituted by alkoxy or phenyl, or cyclohexyl that has optionally been substituted by alkyl,

R³⁹ represents alkyl with 1-6 carbon atoms, unsubstituted or substituted by cyano or alkoxycarbonyl; or it represents cyclohexyl, unsubstituted or substituted by alkyl; or it represents phenyl that is unsubstituted or substituted in each case by halogenalkyl, alkyl, halogen, unsubstituted or substituted phenoxy, phenyl, -SO₂-phenyl, benzyl, carboxy, alkoxy, nitro, cyano and/or alkoxycarbonyl; or it represents benzyl that has optionally been substituted by halogenalkyl, or it represents phenoxycarbonyl that has been substituted by alkoxy, or it represents phenylcarbonyl, or it represents anthraquinonyl, or it represents tetrahydronaphthyl that has been substituted by alkoxy, or it represents phenyl substituted benzotriazole, or it represents naphthyl, or it represents benzodioxolanyl, or it represents thiadiazolyl that has been substituted by alkyl, or it represents morpholinyl, or it represents thiazolyl that has been substituted by halogen and/or cyano,

R³⁸ and R³⁹ together with the nitrogen atom to which they are bonded preferably form a morpholine residue, a pyrrolidine residue, a tetrahydroquinoline residue or a pyrazan residue that has been substituted by one or more alkoxycarbonyl, alkyl and/or oxo substituents,

R⁴⁰ represents alkyl with 1-6 carbon atoms that is unsubstituted or that is substituted by benzyl, alkylcarbonylamino, unsubstituted or morpholinalkyloxy-substituted phenyl, benzyloxy,

cyclopentyl, alkylcarbonyloxy, alkoxycarbonyl, unsubstituted or halogen- and alkyl-substituted phenoxy, alkylcarbonylamino, piperidinyl, alkoxy, dialkylamino, pyridinyl, alkyloxyalkoxy, tetrahydrofuranyl, benzdioxane, imidazolyl, triazolyl, phenylcarbonylamino, benzdioxolane and/or benzthiazolidinethioxolyl,

or it represents phenyl, unsubstituted or substituted by nitro, alkyl, halogen or phenoxy,

or it represents cyclohexyl, unsubstituted or trichlorophenylalkyl-substituted furanyl, dialkyl-substituted isooxolyl, unsubstituted or oxo-substituted tetrahydrofuranyl, alkoxycarbonyl-substituted tetrahydroisoquinoline, dihydrothiophene, oxotetrahydrothiazole, oxo- and alkyl-substituted dihydroimidazolyl, unsubstituted or phenyl-substituted cyclopropyl or cyclopentyl, unsubstituted or cyclopropyl- and hydroxyl-substituted pyridinyl, phenyl- or alkyl- substituted pyrazolyl, pyrazinyl, quinolinyl, tetrahydronaphthalenyl, alkyl-substituted pyrrolyl,

or it represents phenyl-substituted vinyl.

7. Compounds of formula (I), as defined in Claims 1-6, for the prevention and treatment of diseases.

8. Medicaments containing at least one compound of formula (I), as defined in Claim 1, and inert, nontoxic, pharmaceutically acceptable carrier substances, ancillary substances, solvents, vehicles, emulsifiers and/or dispersing agents.

9. Use of compounds of formula (I) and medicaments defined in Claims 1-8 for the prevention and treatment of diseases.

10. Use of compounds of formula (I), as defined in Claims 1-6, for the manufacture of medicaments.

11. Use of compounds of formula (I), as defined in Claims 1-6, for the manufacture of medicaments for the treatment of arteriosclerosis.

12. Process for the prevention and treatment of diseases, characterized by the feature that compounds of formula (I), as defined in Claim 1, are allowed to act on living organisms.

13. Process for the manufacture of medicaments, characterized by the feature that at least one compound of formula (I), as defined in Claim 1, is transformed into a form for application by means of ancillary substances and/or carrier substances.

14. Process for the manufacture of the compounds of formula (I) that are defined in Claim 1, characterized by the feature that reactive phenols are reacted with reactive phenyl derivatives, optionally in the presence of inert solvents and catalysts, and optionally along with isolation of the intermediate products, to give compounds of formulas (I) or (Ia).

INTERNATIONAL SEARCH REPORT

 International Application No.
 PCT/EP 02/06638

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07C233/73 C07C275/36 C07C311/21 A61K31/167 A61K31/17 A61K31/18 C07C271/58		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07C		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPD-Internal, WPI Data, PAJ, INSPEC, COMPENDEX, BEILSTEIN Data, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 393 470 A (BAYER AG) 7 May 1975 (1975-05-07) claims 1,2,4-6,8,9,12,13,16-18	1-3,5,6
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-/-		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *&* document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
8 November 2002		15/11/2002
Name and mailing address of the ISA European Patent Office, P.O. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Seelmann, M

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 02/06638

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 00 73265 A (YOUNGQUIST ROBERT SCOTT ;MCIVER JOHN MCMILLAN (US); UNIV TEXAS SOU) 7 December 2000 (2000-12-07) cited in the application page 13 -page 15 page 17 -page 22; examples 5,7,9,11,13 Page 45, Section: "uses of the present compounds" - Claims 1-8	1-3, 5-10, 12-14
X	WO 00.72920 A (YOUNGQUIST ROBERT SCOTT ;MCIVER JOHN MCMILLAN (US); UNIV TEXAS SOU) 7 December 2000 (2000-12-07) page 13 -page 15 Page 38, Section: "uses of the present compounds" claims 1-7; examples 2-6,9,11-14,16,17	1-10, 12-14
X,P	WO 01 60784 A (BRISTOL MYERS SQUIBB CO ;RYONO DENNIS E (US); ZHANG MINSHENG (US);) 23 August 2001 (2001-08-23) page 10, line 25 -page 11, line 11; claims 1-23; examples 1-19	1-14
X	US 4 181 519 A (PILGRAM KURT H G ET AL) 1 January 1980 (1980-01-01) Table 1, Column 9-10, Example 31-32 Claims 1-4, 10	1-3,5,6

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International Application No

PCT/EP 02/06638

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Information on patent family members

Int. National Application No.

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INTERNATIONAL SEARCH REPORT

International filing number
PCT/EP 02/06638

Field 1 Comments regarding to the claims that have proven to be nonsearchable
(continuation of point 2 on page 1)

In accordance with Article 17(2)a), a search report has not been compiled for certain claims for the following reasons:

1. ☒ Claim Nos.
 because they pertain to subjects in regard to which the authorities are not obliged to conduct a search, namely

Although Claim Nos. 9 and 12 pertain to a process for the treatment of a human/animal body, a search has been carried out and was based on the stated effects of the compound/composition.

2. ☐ Claim Nos.
 because they pertain to portions of the international patent application that correspond so little to the prescribed requirements that a meaningful international search cannot be carried out, namely

3. ☐ Claim Nos.
 because they pertain to subordinate claims that have not been drawn up in accordance with clauses 2 and 3 of Regulation 6.4 a).

Field II Comments regarding deficient uniformity of the invention (continuation of point 3 on page 1)

The international search authorities have found that this international patent application contains several inventions:

1. ☐ Since the applicant has paid all the required additional search fees in a timely manner, this international search report covers all the claims that are searchable.

2. ☐ Since the search could not be carried out for all the researchable claims without the expenditure of time that would have justified an additional search fee, the authorities have not required the payment of such a fee.

3. ☐ Since the applicant has paid only some of the required additional search fees in a timely manner, this international search report covers only the claims for which fees have been paid, namely Claim Nos.:

4. ☐ The applicant has not paid the required additional search fees in a timely manner. The international search report is therefore restricted to the invention that is mentioned first in the claims; this is included in the following claims:

Comments regarding an objection ☐ The additional fees were paid by the applicant with an objection being filed.

☐ The payment of the additional fees took place without any objection.